

## PATENT COOPERATION TREATY

PCT

## NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner  
US Department of Commerce  
United States Patent and Trademark  
Office, PCT  
2011 South Clark Place Room  
CP2/5C24  
Arlington, VA 22202  
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 14 February 2001 (14.02.01)	
International application No. PCT/GB00/02513	Applicant's or agent's file reference 44.95.70360/008
International filing date (day/month/year) 29 June 2000 (29.06.00)	Priority date (day/month/year) 29 June 1999 (29.06.99)
Applicant TJØTTA, Enok et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:

05 January 2001 (05.01.01)

☐ in a notice effecting later election filed with the International Bureau on:2. The election ☒ was☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Olivia TEFY
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

# PATENT COOPERATION TREATY

From the  
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

COCKBAIN, Julian  
FRANK B. DEHN & CO.  
179 Queen Victoria Street  
London EC4V 4EL  
GRANDE BRETAGNE

FILE 70360/008  
- 9 AUG 2001  
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## PCT

NOTIFICATION OF TRANSMITTAL OF  
THE INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing  
(day/month/year) 07.08.2001

Applicant's or agent's file reference  
44.70360/008

### IMPORTANT NOTIFICATION

International application No.  
PCT/GB00/02513

International filing date (day/month/year)  
29/06/2000

Priority date (day/month/year)  
29/06/1999

Applicant  
A-VIRAL AS et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.


#### 4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/

 European Patent Office  
D-80298 Munich  
Tel. +49 89 2399 - 0 Tx: 523656 epmu d  
Fax: +49 89 2399 - 4465

Authorized officer

Ambroa, J.R.

Tel. +49 89 2399-8012



# PATENT COOPERATION TREATY

## PCT

### INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference <b>44.70360/008</b>	<div style="display: flex; justify-content: space-between;"> <div style="width: 40%;"> <b>FOR FURTHER ACTION</b> </div> <div style="width: 60%; font-size: small;">           See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)         </div> </div>	
International application No. <b>PCT/GB00/02513</b>	International filing date (day/month/year) <b>29/06/2000</b>	Priority date (day/month/year) <b>29/06/1999</b>
International Patent Classification (IPC) or national classification and IPC <b>C07D231/32</b>		
Applicant <b>A-VIRAL AS et al.</b>		
<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 8 sheets, including this cover sheet.</p> <p><input checked="" type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of 7 sheets.</p>		
<p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"> <li>I <input checked="" type="checkbox"/> Basis of the report</li> <li>II <input type="checkbox"/> Priority</li> <li>III <input checked="" type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</li> <li>IV <input type="checkbox"/> Lack of unity of invention</li> <li>V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</li> <li>VI <input type="checkbox"/> Certain documents cited</li> <li>VII <input checked="" type="checkbox"/> Certain defects in the international application</li> <li>VIII <input type="checkbox"/> Certain observations on the international application</li> </ul>		
Date of submission of the demand  <b>05/01/2001</b>	Date of completion of this report  <b>07.08.2001</b>	
Name and mailing address of the international preliminary examining authority:  <div style="display: flex; align-items: center;"> <div>             European Patent Office              D-80298 Munich              Tel. +49 89 2399 - 0 Tx: 523656 epmu d              Fax: +49 89 2399 - 4465           </div> </div>	Authorized officer  <b>Feiler, L</b>  Telephone No. +49 89 2399 8282	



**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/GB00/02513

**I. Basis of the report**

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

**Description, pages:**

1-21 as originally filed

**Claims, No.:**

1-23 as received on 17/07/2001 with letter of 13/07/2001

**Drawings, sheets:**

1/5-5/5 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/GB00/02513

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 2-10, 21-23.

because:

☒ the said international application, or the said claims Nos. 2-10, 21-23 relate to the following subject matter which does not require an international preliminary examination (*specify*):  
**see separate sheet**

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)

Yes: Claims 1-10, 12-23

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/GB00/02513

	No:	Claims	11
Inventive step (IS)	Yes:	Claims	20
	No:	Claims	1-19, 21-23
Industrial applicability (IA)	Yes:	Claims	1, 11-20
	No:	Claims	

2. Citations and explanations  
**see separate sheet**

**VII. Certain defects in the international application**

The following defects in the form or contents of the international application have been noted:  
**see separate sheet**

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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International application No. PCT/GB00/02513

1. The new claims are acceptable except Claim 13 which lacks the definition of  $R_2$  as having upto 10 C-atoms. The rest of the characteristics are based on original Claim 14 page 4 and 5, second paragraphs.

Claim 1 on file is based on original Claim 1 and on page 3, last paragraph, page 4 top and on page 5, second paragraph of the original description. Claims 2-10 correspond to original claims 2-10. Claim 11 is based on original Claim 11, page 1, first paragraph and page 3, last paragraph.

Claims 14-21 are based on corresponding original claims.

The same applies to the second Claim 21 and Claim 24 which should obviously read Claims 22 and 23.

2. Claims 2-10 and 21-23 (partly renumbered, see above) relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

**3. Cited Documents**

Mol. Pharm. 34 (1988), pp. 186-193= D1  
Biochem. Biophys. Res. Comm. 63 (1975)= D2  
Pharmacol. Pharm. 30 (1978), pp. 833-843= D3  
J. Chromatography 277 (1983), pp. 408-413= D4  
Analyst 110 (1985), pp. 1289-1293= D5  
Biochem. Pharm. 35 (1986), pp. 3935-3939= D6  
Boll. Chim. Pharm. 126 (1987), pp. 244-245= D7  
Eur. J. Med. Chem. 17 (1982), pp. 429-432= D8  
Ceskosl. Farm. 24 (1975), pp. 128-132= D9  
Chem. Pharm. Bull. 20 (1972), pp. 1862-1868= D10  
Australian J. Chem. 28 (1975), pp. 421-426= D11  
Can. J. Pharm. Sci. 2 (1967), pp. 22-24= D12  
Chem. Abs. 54 (1960), 22587h= D13  
Chem. Abs. 41 (1957), 10491d= D14  
DE-A-2022712= D15  
US-A-3629282= D16  
US-A-4956377= D17

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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International application No. PCT/GB00/02513

US-A-4169147= D18

US-A-3968219= D19

The indicated designation will be used throughout the examination procedure.

#### **4. Novelty**

D15 differs essentially from subject matter claimed in that the 4-position bears a thiocyanate moiety. The difference between the D16 compounds and the claims on file resides in the presence of a polyoxymethylene moiety in 4-position not considered according to the application.

D17 discloses the antiviral activity of phenylbutazon differing from compounds claimed mainly due to the absence of OH or SH in 4-position.

D18 discloses compounds bearing an ether function in 3-position being prodrugs of phenylbutazon and oxyphenbutazones.

D19 discloses bis-hydroxyphenylbutazone esters which do not consider an OH or SH group in 4-position of the pyrazoldione.

Use Claim 1 and method Claim 2 appear to be novel in view of D1 and D2 and also D14. D1 classifies 4-hydroperoxy- and 4-hydroxyphenylbutazone as ineffective prostaglandin H synthase inhibitors. D2 teaches that the oxygenated oxyphenbutazone (4-hydroxy- oxyphenbutazone) is not an inhibitor of prostaglandin biosynthesis.

D14 discloses that e.g. 4-hydroxy-3,5-dioxo-1,2diphenylpyrazolidine has no significant antiinflammatory activity.

On the other hand it would appear that Claim 11 is not novel since D14 already discloses a solution of 4-hydroxy-3,5-dioxo-1,2diphenylpyrazolidine in ethanol (left column).

Due to the effected restriction product Claims 13-20 may be considered to be novel over D2-D14.

Claim 13 comprises 2 provisos which appear to correspond to the compound disclosed on the bottom of page 754 of D2 and to compounds I and IV on page 1290 of D5.

The following observations apply to subject matter which can be considered to be novel.

## **5. Inventive Step - Breadth of Claims**

### **5.1 Subjective Problem**

According to the application (p. 1, first paragraph and the paragraph bridging pages 1 and 2) the problem underlying the invention is to be seen in the provision of compounds which have improved antiviral activity and are useful to treat HIV.

### **5.2 Relevant and closest prior art**

It would appear that in documents D1-D16 as well as D18 and D19 antiviral activity of the disclosed compounds is not mentioned. On the other hand D17 discloses such activity of phenylbutazon. Consequently, this document is considered to be the closest prior art.

### **5.3 Objectively solved problem and evaluation**

According to example 12 and fig. 1 comparative data have been provided whereby 4-hydroxy-oxyphenbutazon has been compared with the closest prior art phenbutazon of D17. On the basis of this data 4-hydroxy-oxyphenbutazon can be considered to be inventive.

### **5.4 Breadth of the claims**

The breadth should be such that it can be assumed that all the comprised possibilities actually solve the problem underlying the invention on which an inventive step could be based. It is true that a reasonable generalisation over the findings is acceptable but in the present case this possibility is rather limited since the acknowledgement of an inventive step is to be based on a **quantitative** effect. In Claim 1 the following definitions are certainly unreasonable: Ar<sup>1</sup> and Ar<sup>2</sup> as "homo or heterocyclic aromatic group.....". It would also appear that OH substitution of Ar<sup>1</sup> or Ar<sup>2</sup> are essential for the activity. Specifically, it is not considered that H, CN, Cl, F and Br are equivalents to OH. In the absence of corresponding favourable data the hydroperoxy derivatives as well as the S-analogues of these compounds cannot be considered to solve the above defined problem. Consequently, such compounds cannot be considered to be inventive. D17 discloses phenbutazon as antivirally active compound. Due to its close structural relationship between the compounds referred to in the claims of the application (metabolites!) the solution to the problem to just provide alternative antivirally active compounds must be considered to be obvious for the person skilled in the art. An inventive step can therefore not be acknowledged over the proposed broadness of the claims which could be considered to be novel. It should also be taken into consideration (see specifically Claims 1 and 2) that D14

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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International application No. PCT/GB00/02513

discloses that derivatives of phenylbutazone did not reveal significant antiinflammatory activity.

**6. Industrial applicability**

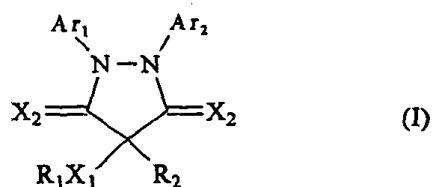
For the assessment of the present claims 2-10 and 21-23 (renumbered) on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

**7. The description has not been adapted to the claims**

70360pcl.605

Claims

1. The use of a compound of formula I



(where each  $X_2$ , which may be the same or different is O or S,

$X_1$  is O, OO or S,

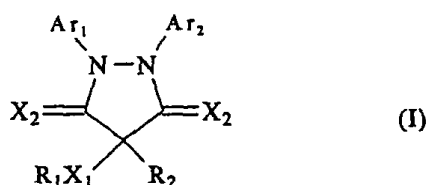
$R_1$  is hydrogen or a hydroxyl or thiol protecting group,

$R_2$  is hydrogen or a alkyl, alkenyl, alkynyl, alkaryl, aralkyl or aralkenyl group, containing up to 10 carbons, optionally substituted by a sulphonyl group, and each of

$Ar_1$  and  $Ar_2$ , which may be the same or different, is a homo or heterocyclic aromatic group comprising 5 to 7 membered aromatic ring, optionally carrying a fused aromatic ring and optionally substituted on ring atoms by  $C_{1-6}$  alkyl, hydroxy, thiol,  $C_{1-6}$  alkoxy, cyano, Cl, F, Br, I, protected hydroxy, or protected thiol), or a physiologically acceptable salt thereof, for the manufacture of a medicament for use in therapy or prophylaxis.

2. A method of treatment of the human or non-human body to combat an inflammatory or viral disease, which method comprises administering to said body a compound of formula I

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(where each  $X_2$ , which may be the same or different is O or S,

$X_1$  is O, OO or S,

$R_1$  is hydrogen or a hydroxyl or thiol protecting group,  
 $R_2$  is hydrogen or a alkyl, alkenyl, alkynyl, alkaryl, aralkyl or aralkenyl group, containing up to 10 carbons, optionally substituted by a sulphonyl group, and each of  $Ar_1$  and  $Ar_2$ , which may be the same or different, is a homo or heterocyclic aromatic group comprising 5 to 7 membered aromatic ring, optionally carrying a fused aromatic ring and optionally substituted on ring atoms by  $C_{1-6}$  alkyl, hydroxy, thiol,  $C_{1-6}$  alkoxy, cyano, Cl, F, Br, I, protected hydroxy, or protected thiol), or a physiologically acceptable salt thereof.

3. A method as claimed in claim 2 comprising administering said compound, or a physiologically acceptable salt thereof in combination with another antiviral agent.

4. A method as claimed in claim 3 wherein said additional antiviral agent is at least one antiviral agent selected from a reverse transcriptase inhibitor and a protease inhibitor.

5. A method as claimed in claim 3 wherein said additional antiviral agent is an agent selected from the group of AZT, indinavir, nevirapine and 2',3'-dideoxyinosine (ddI).

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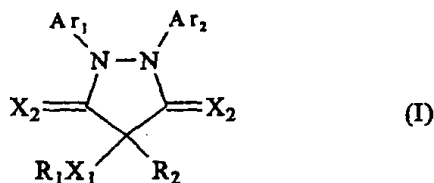
6. A method as claimed in any of claims 2 to 5 wherein said disease is a disease caused by a pathogen from the group of togaviridea, reoviridea, picornaviridea, hantaviridea, orthomyxoviridea, paramyxoviridea, mononegaviralis, viral hepatitis, haemorrhagic fevers, flaviviridea, viral encephalitis, coronaviridea, calciviridea, adenoviridea, papovaviridea, arboviridea, pox virus, rhabdoviridea, arenaviridea HIV-1, HIV-2, HTLV-I, HTLV-II and herpes viruses.

7. A method of combatting HIV infection which comprises administering to an HIV-infected patient a T-lymphocyte growth suppressing agent in an amount sufficient to suppress T-lymphocyte growth in said patient for a period sufficient to reduce the T-lymphocyte concentration in the lymphatic system in said patient by at least 25% said administration being repeated at intervals of at least 3 months.

8. A method of combatting HIV infection as claimed in claim 7 wherein said T-lymphocyte growth suppressing agent is a pyrazolidinol.

9. A method as claimed in claim 7 or claim 8 wherein said interval is at least 9 months.

10. A method as claimed in any of claims 7 to 9 wherein a compound of formula I



(where each  $\text{X}_2$ , which may be the same or different is O or S,

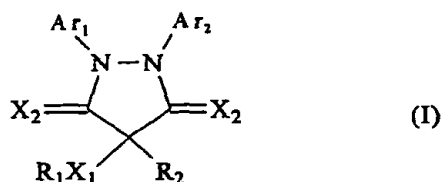
- 25 -

$X_1$  is O, OO or S,

$R_1$  is hydrogen or a hydroxyl or thiol protecting group,

$R_2$  is hydrogen or a alkyl, alkenyl, alkynyl, alkaryl, aralkyl or aralkenyl group, containing up to 10 carbons, optionally substituted by a sulphonyl group, and each of  $Ar_1$  and  $Ar_2$ , which may be the same or different, is a homo or heterocyclic aromatic group comprising 5 to 7 membered aromatic ring, optionally carrying a fused aromatic ring and optionally substituted on ring atoms by  $C_{1-6}$  alkyl, hydroxy, thiol,  $C_{1-6}$  alkoxy, cyano, Cl, F, Br, I, protected hydroxy, or protected thiol), or a physiologically acceptable salt thereof is administered in a daily dose of 0.1 to 10  $\mu\text{mol/kg}$  bodyweight.

11. A pharmaceutical composition comprising a compound of formula I



(where each  $X_2$ , which may be the same or different is O or S,

$X_1$  is O, OO or S,

$R_1$  is hydrogen or a hydroxyl or thiol protecting group,

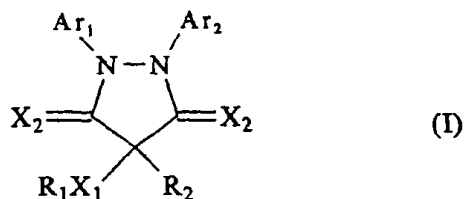
$R_2$  is hydrogen or a alkyl, alkenyl, alkynyl, alkaryl, aralkyl or aralkenyl group, containing up to 10 carbons, optionally substituted by a sulphonyl group, and each of  $Ar_1$  and  $Ar_2$ , which may be the same or different, is a homo or heterocyclic aromatic group comprising 5 to 7 membered aromatic ring, optionally carrying a fused aromatic ring and optionally substituted on ring atoms by  $C_{1-6}$  alkyl, hydroxy, thiol,  $C_{1-6}$  alkoxy, cyano, Cl, F, Br, I, protected hydroxy, or protected thiol), or a physiologically acceptable salt thereof, together with

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at least one pharmaceutically acceptable carrier or excipient.

12. A pharmaceutical composition as claimed in claim 11 additionally comprising another antiviral agent.

13. A compound of formula I



(where each  $X_2$ , which may be the same or different is O or S,

$X_1$  is O, OO or S,

$R_1$  is hydrogen or a hydroxyl or thiol protecting group,

$R_2$  is hydrogen or a alkyl, alkenyl, alkynyl, alkaryl, aralkyl or aralkenyl group, optionally substituted by a sulphonyl group, and

one of  $Ar_1$  and  $Ar_2$  is Ph and the other is 4-hydroxyphenyl,

or a salt thereof, providing that if  $R_2$  is  $C_4H_9$ ,  $R_1$  is not H or OH.

14. A compound as claimed in claim 13 or claim 14 wherein one  $X_2$  group is S.

15. A compound as claimed in either of claims 13 or 14 wherein  $X_1$  is O.

16. A compound as claimed in any of claims 13 to 15 wherein  $R_1$  is acyl.

17. A compound as claimed in any of claims 13 to 16 wherein  $R_1$  is hydrogen.

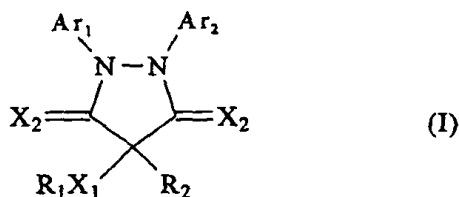
- 27 -

18. A compound as claimed in claim 13 wherein each  $X_2$  is oxygen,  $R_1X_1$  is HO or  $CH_3CO.O$ , and  $R_2$  is  $C_{1-6}$  alkyl or alkenyl, or a salt thereof.

19. A compound as claimed in any of claims 13 to 18 for use as a medicament.

20. 4-Butyl-4-hydroxy-2(p-hydroxyphenyl)-1-phenyl-3,5-pyrazolidinedione for use as a medicament.

21. A method of treatment of the human or non-human body to combat an autoimmune disease or tissue rejection, which method comprises administering to said body a compound of formula I



(where each  $X_2$ , which may be the same or different is O or S,  
 $X_1$  is O, OO or S,  
 $R_1$  is hydrogen or a hydroxyl or thiol protecting group,  
 $R_2$  is hydrogen or a alkyl, alkenyl, alkynyl, alkaryl, aralkyl or aralkenyl group, containing up to 10 carbons, optionally substituted by a sulphonyl group, and each of  $Ar_1$  and  $Ar_2$ , which may be the same or different, is a homo or heterocyclic aromatic group comprising 5 to 7 membered aromatic ring, optionally carrying a fused aromatic ring and optionally substituted on ring atoms by  $C_{1-6}$  alkyl, hydroxy, thiol,  $C_{1-6}$  alkoxy, cyano, Cl, F, Br, I, protected hydroxy, or protected thiol) or a physiologically tolerable salt thereof.

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21. A method of claim 21 wherein said disease is selected from Addison's disease, Behçet's syndrome, diabetes mellitus, haemolytic anaemia, lupus erythematosus, multiple sclerosis, myasthenia gravis, pernicious anaemia, polyglandular deficiency, polymyositis, dermatomyositis, testicular failure, thrombocytopenic purpura, Crohns disease, ulcerative colitis and rheumatoid arthritis.

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24. A method of claim 21 wherein said tissue rejection is tissue rejection following transplant.

# PATENT COOPERATION TREATY

CG

From the:  
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

COCKBAIN, Julian  
FRANK B. DEHN & CO.  
179 Queen Victoria Street  
London EC4V 4EL  
GRANDE BRETAGNE

PCT

File

70360/008

19 MAR 2001

WRITTEN OPINION

(PCT Rule 66)

Date of mailing  
(day/month/year)

14.03.2001

Applicant's or agent's file reference

44.70360/008

REPLY DUE

within 3 month(s)  
from the above date of mailing

International application No.

PCT/GB00/02513

International filing date (day/month/year)

29/06/2000

Priority date (day/month/year)

29/06/1999

International Patent Classification (IPC) or both national classification and IPC

C07D231/32

Applicant

A-VIRAL AS et al.

1. This written opinion is the first drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

- I ☒ Basis of the opinion
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain document cited
- VII ☒ Certain defects in the international application
- VIII ☒ Certain observations on the international application

CG Called  
Hutterer  
- extension of  
1 month  
EPC will  
write to  
confirm  
12/6/01  
CG

3. The applicant is hereby invited to reply to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4.  
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.  
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 29/10/2001.

DUE DATES  
NOTED

14/6/01

Name and mailing address of the international preliminary examining authority:

European Patent Office  
D-80298 Munich  
Tel. +49 89 2399 - 0 Tx: 523656 epmu d  
Fax: +49 89 2399 - 4465

Authorized officer / Examiner

Feiler, L

Formalities officer (incl. extension of time limits)

Hutterer, G

Telephone No. +49 89 2399 8066



## WRITTEN OPINION

International application No. PCT/GB00/02513

### I. Basis of the opinion

1. This opinion has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed"*):

#### Description, pages:

1-21 as originally filed

#### Claims, No.:

1-26 as originally filed

#### Drawings, sheets:

1/5-5/5 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
  - ☐ the language of publication of the international application (under Rule 48.3(b)).
  - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).
3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:
- ☐ contained in the international application in written form.
  - ☐ filed together with the international application in computer readable form.
  - ☐ furnished subsequently to this Authority in written form.
  - ☐ furnished subsequently to this Authority in computer readable form.
  - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
  - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.
4. The amendments have resulted in the cancellation of:
- ☐ the description, pages:
  - ☐ the claims, Nos.:

## WRITTEN OPINION

International application No. PCT/GB00/02513

- ☐ the drawings, sheets:
5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):
- (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

### III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:
- ☐ the entire international application,
- ☒ claims Nos. 2-10, 24-26,

because:

- ☒ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):  
**see separate sheet**
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the said claims Nos. .
2. A written opinion cannot be drawn due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:
- ☐ the written form has not been furnished or does not comply with the standard.
- ☐ the computer readable form has not been furnished or does not comply with the standard.

### V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement
- |                     |   |
|---------------------|---|
| Novelty (N)         | Claims 1, 2, 11, 13-17, 19-23 no; 12, 18, 24-26 |
| Inventive step (IS) | Claims 1-26, no                                 |

## WRITTEN OPINION

International application No. PCT/GB00/02513

---

Industrial applicability (IA)      Claims    1, 11-23, yes

2. Citations and explanations  
**see separate sheet**

### VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:  
**see separate sheet**

### VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:  
**see separate sheet**

1. Claims 2-10 and 24-26 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Claim 13 is unclear. It is understood that the O attached to the pyrazolidine ring may also be replaced by S.

## **2. Cited Documents**

Mol. Pharm. 34 (1988), pp. 186-193= D1  
Biochem. Biophys. Res. Comm. 63 (1975)= D2  
Pharmacol. Pharm. 30 (1978), pp. 833-843= D3  
J. Chromatography 277 (1983), pp. 408-413= D4  
Analyst 110 (1985), pp. 1289-1293= D5  
Biochem. Pharm. 35 (1986), pp. 3935-3939= D6  
Boll. Chim. Pharm. 126 (1987), pp. 244-245= D7  
Eur. J. Med. Chem. 17 (1982), pp. 429-432= D8  
Ceskosl. Farm. 24 (1975), pp. 128-132= D9  
Chem. Pharm. Bull. 20 (1972), pp. 1862-1868= D10  
Australian J. Chem. 28 (1975), pp. 421-426= D11  
Can. J. Pharm. Sci. 2 (1967), pp. 22-24= D12  
Chem. Abs. 54 (1960), 22587h= D13  
Chem. Abs. 41 (1957), 10491d= D14  
DE-A-2022712= D15  
US-A-3629282= D16  
US-A-4956377= D17  
US-A-4169147= D18  
US-A-3968219= D19

The indicated designation will be used throughout the examination procedure.

## **3. Novelty**

D15 differs essentially from subject matter claimed in that 4-position bears a

thiocyanate moiety. The difference between the D16 compounds and those claims resides in the presence of a polyoxymethylene moiety in 4-position instead of an OH group.

D17 disclose the antiviral activity of phenylbutazon differing from compounds claimed mainly due to the absence of OH or SH in 4-position.

D18 discloses compounds bearing an ether function in 3-position being prodrugs of phenylbutazon and oxyphenbutazones.

D19 discloses bis-hydroxyphenylbutazone esters which do not consider an OH or SH group in 4-position of the pyrazoldione.

On the other hand use Claim 1, method Claim 2 as well as product Claims 13,14, 16, 17, 19, 21 and 22 are not novel in view of D1 (see page 191, scheme 1 and pp. 191-192).

Subject matter of Claims 13, 14, 17, 20, and 22 is also not novel in view of D2 (see p. 754, fig. 2).

The following documents destroy the novelty of Claims 13-15, 17 and 19:

D3 (see compound 6)

D4 (see compound 7)

D5 (see compounds I and IV of table 1)

D6 (see fig. 2, 3 and 5)

D7 (see compound 4)

D8 (see compound 13 and page 432, left-hand column, lines 1-5)

D9 (see formula on page 130, right-hand column)

D10 (see compounds 15-23 of table III)

D11 (see formula (2))

D12 (see page 22, formula I)

D13 and D14.

Claim 15 comprises 34 disclaimers. The Applicant is requested to indicate the corresponding prior art.

The following observations apply to claims which do not comprise known matter.

#### **4. Inventive Step - Breadth of Claims**

##### **4.1 Subjective Problem**

According to the application (p. 1, first paragraph and the paragraph bridging pages 1 and 2) the problem underlying the invention is to be seen in the provision of compounds

which have improved antiviral activity and are useful to treat HIV.

#### 4.2 Relevant and closest prior art

It would appear that in documents D1-D16 as well as 18 and 19 antiviral activity of the disclosed compounds is not mentioned. On the other hand D17 discloses such activity of phenylbutazon. Consequently, this document is considered to be the closest prior art.

#### 4.3 Objectively solved problem

According to example 12 and fig. 1 comparative data have been provided whereby 4-hydroxy-oxyphenbutazon has been compared with the closest prior art phenbutazon of D17. The data are irrelevant because the definition of Ar1 and Ar2 as " homo or heterocyclic aromatic group" (see Claim 14) does not comprise substituents thereof. It can therefore only be said that the problem which has been solved by certain compounds is the provision of compounds which are antivirally active.

#### 4.4 Evaluation of the solution of the problem

D17 discloses phenbutazon as antivirally active compound. Due to its close structural relationship between the compounds referred to in the claims of the application (metabolites!) the solution to the problem defined in point 4.3 must be considered to be obvious for the person skilled in the art.

An inventive step can therefore not be acknowledged over the proposed broadness of the claims which could be considered to be novel.

#### 4.5 Suggestions for overcoming the objections according to point 4.4

An inventive step could nevertheless be acknowledged should convincing comparative data be submitted which show that the technical problem defined in point 4.1 has actually been solved.

In this respect it should be borne in mind that the compounds of the closest prior must bear the closest possible structural resemblance in order that the comparison be valid. A suitable comparison would be e.g. 4-hydroxy-phenbutazon versus phenbutazon. The hydroperoxy derivatives as well as the S-analogues are also to be included in the comparative tests.

#### 4.6 Breadth of the claims

The breadth should be such that it can be assumed that all the comprised possibilities actually solve the problem underlying the invention on which an inventive step could be based. It is true that a reasonable generalisation over the findings is acceptable but in the present case this possibility is rather limited since the acknowledgement of an

inventive step is to be based on a quantitative effect. The following definitions are certainly unreasonable: "4-hydroxy or hydroperoxy-3,5-dioxo-pyrazolidine or an equivalent" without definition of the further substituents, "homo or heterocyclic aromatic group".

### **5. Industrial applicability**

For the assessment of the present claims 2-10 and 24-26 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

### **6. Formulation of the claims**

- In use claims the formula of the compounds should be clearly indicated.
- Claim 15 comprises 34 disclaimers which is not acceptable (lack of ready comprehensibility).
- Furthermore Claim 15 refers to Claim 14 but excludes compounds which are not comprised by Claim 14 (Ar1 cannot be H according to Claim 14 and N-methyl-piperidin-4-yl is not aromatic).

### **7. Description**

The description should be adapted to the new claims in the framework of the original disclosure.

Any examples and parts of the description no longer encompassed by Claim 1 are to be deleted.

The documents cited in this communication should, insofar as this has not taken place, be referred to in the description with a short indication of their contents.

Pages amended in handwriting should also be submitted retyped.

(19) World Intellectual Property Organization  
International Bureau



(43) International Publication Date  
4 January 2001 (04.01.2001)

PCT

(10) International Publication Number  
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231/30, A61K 31/4152, A61P 31/08, 37/06

(NO). KLAVENESS, Jo [NO/NO]; A-Viral AS, Karihaugveien 102, N-1006 Oslo (NO).

(21) International Application Number: PCT/GB00/02513

(74) Agents: COCKBAIN, Julian et al.; Frank B. Dehn & Co.,  
179 Queen Victoria Street, London EC4V 4EL (GB).

(22) International Filing Date: 29 June 2000 (29.06.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
9915184.7 29 June 1999 (29.06.1999) GB

(71) Applicant (for all designated States except US): A-VIRAL  
AS [NO/NO]; Karihaugveien 102, N-1006 Oslo (NO).

(81) Designated States (national): AE, AG, AL, AM, AT, AT (utility model), AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, CZ (utility model), DE, DE (utility model), DK, DK (utility model), DM, DZ, EE, EE (utility model), ES, FI, FI (utility model), GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KR (utility model), KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK (utility model), SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(71) Applicant (for GB only): COCKBAIN, Julian [GB/GB];  
Flat 4, 83 Linden Gardens, London W2 4EU (GB).

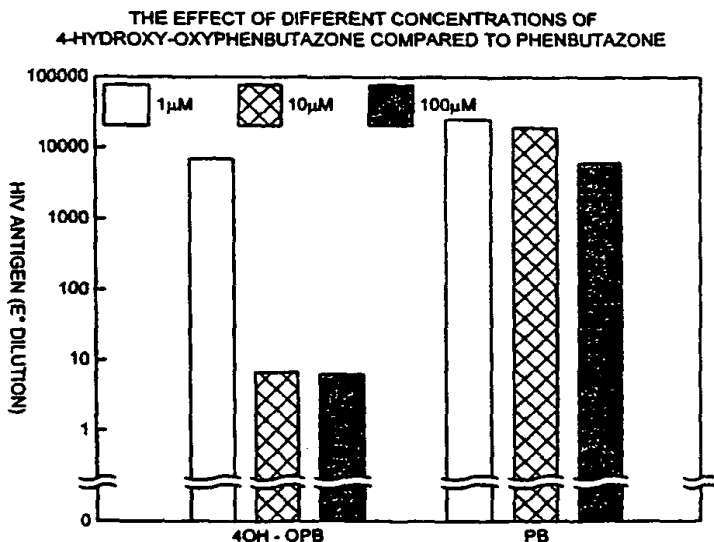
(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

(72) Inventors; and

(75) Inventors/Applicants (for US only): TJØTTA, Enok  
[NO/NO]; A-Viral AS, Karihaugveien 102, N-1006 Oslo

[Continued on next page]

(54) Title: PYRAZOLIDINOL COMPOUNDS



(57) Abstract: The invention provides the use of an optionally hydroxy-protected 4-hydroxy or hydroperoxy-3,5-dioxypyrazolidine or an equivalent wherein a pyrazolidine ring attached oxygen is replaced by a sulphur, or a physiologically acceptable salt thereof, for the manufacture of a medicament for use in therapy or prophylaxis. Additionally, the invention provides a method of combatting HIV infection which comprises administering to an HIV-infected patient a T-lymphocyte growth suppressing agent, preferably a pyrazolidinol, in an amount sufficient to suppress T-lymphocyte growth in said patient for a period sufficient to reduce the T-lymphocyte concentration in lymph nodes in said patient by at least 25 % said administration being repeated at intervals of at least 3 months.

# INTERNATIONAL SEARCH REPORT

International Application No.

PCT/GB 00/02513

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D231/32 C07D231/30 A61K31/4152 A61P31/08 A61P37/06

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	M. F. HUGHES ET AL.: MOLECULAR PHARMACOLOGY, vol. 34, no. 2, 1988, pages 186-93, XP000925977 page 186, summary; page 191, scheme 1; page 191-192	1,2,13, 14,16, 17,19, 21,22
X	P. S. PORTOGHESE ET AL.: BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 63, no. 3, 1975, pages 748-55, XP000925976 page 748 page 751 -page 752 page 754, figure 2	13,14, 17,20,22
	--- -/-- ---	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

20 October 2000

Date of mailing of the international search report

06/11/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3018

Authorized officer

Hass, C

# INTERNATIONAL SEARCH REPORT

Internat. Application No.

PCT/GB 00/02513

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages,	Relevant to claim No.
X	R. WACHOWIAK: POL. J. PHARMACOL. PHARM., vol. 30, no. 6, 1978, pages 833-43, XP000925975 page 841, compound 6 ---	13-15, 17,19
X	J. X. DE VRIES ET AL.: JOURNAL OF CHROMATOGRAPHY, vol. 277, 1983, pages 408-13, XP000925974 page 408, compound 7 ---	13-15, 17,19
X	H. FABRE ET AL.: ANALYST, vol. 110, no. 1, November 1985 (1985-11), pages 1289-93, XP000925972 page 1290, table 1, compounds I and IV ---	13,14, 17,19
X	S. ICHIHARA ET AL.: BIOCHEMICAL PHARMACOLOGY, vol. 35, no. 22, 1986, pages 3935-9, XP000925971 page 3937, figures 2 and 3; page 3938, figure 5 ---	13,14, 17,19
X	G. FACCHINI ET AL.: BOLL. CHIM. PHARM., vol. 126, no. 6, 1987, pages 244-5, XP000925970 page 244, compound 4 ---	13,14, 17,19
X	D. RAHTZ ET AL.: EUR. J. MED. CHEM. - CHIM. THER., vol. 17, no. 5, 1982, pages 429-32, XP000925964 page 430, right-hand column, compound 13; page 432, left-hand column, lines 1-5 ---	13,14, 17,19
X	M. PETERKOVA ET AL.: CESKOSLOVENSKA FARMACIE, vol. 24, no. 3, 1975, pages 128-32, XP000925980 page 130, right-hand column, chemical formula ---	13,14, 17,19
X	O. AKI ET AL.: CHEMICAL AND PHARMACEUTICAL BULLETIN, vol. 20, no. 9, 1972, pages 1862-8, XP000925979 page 1864, table III, compounds 15-23 ---	13-15, 17,19
X	M. WOODRUFF ET AL.: AUSTRALIAN JOURNAL OF CHEMISTRY, vol. 28, no. 2, 1975, pages 421-6, XP000952038 page 422, formula (2) and corresponding definitions in the text ---	13,14, 17,19
	-/--	

# INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 00/02513

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	R. T. COUTTS ET AL.: CANADIAN JOURNAL OF PHARMACEUTICAL SCIENCES, vol. 2, no. 1, 1967, pages 22-4, XP000952039 page 22, formula I ---	13,14, 17,19
X	CHEMICAL ABSTRACTS, vol. 54, no. 21, 10 November 1960 (1960-11-10) Columbus, Ohio, US; abstract no. 22587h, column 22587; XP002150571 22587h, 22588d & G. ADEMBRI ET AL.: GAZZ. CHIM. ITAL., vol. 89, 1959, pages 700-9, ---	13,14, 17,19
X	CHEMICAL ABSTRACTS, vol. 51, no. 14, 25 July 1957 (1957-07-25) Columbus, Ohio, US; abstract no. 10491d, column 10491; XP002150572 10491h, 10491i, 10492a, 10492b & K. M. HAMMOND ET AL.: J. CHEM. SOC., 1957, pages 1062-7, ---	13,14, 17,19
A	DE 20 22 712 A (DR. THIEMANN GMBH CHEM.-PHARM. FABRIK) 25 November 1971 (1971-11-25) claims 1,2 ---	1,2,11, 13-15,22
A	US 3 629 282 A (NEGREVERGNE GEORGES) 21 December 1971 (1971-12-21) abstract; claim 1 ---	1,2,11, 13-15,22
A	US 4 956 377 A (MIESCH JEAN-OLIVIER) 11 September 1990 (1990-09-11) cited in the application claims ---	1,2,6-8, 24
A	US 4 169 147 A (BODOR NICHOLAS S ET AL) 25 September 1979 (1979-09-25) cited in the application abstract & US 4 139 709 A 13 February 1979 (1979-02-13) cited in the application & US 4 117 232 A cited in the application & US 4 036 845 A cited in the application & US 3 957 803 A cited in the application ---	1,2,11
	-/--	

# INTERNATIONAL SEARCH REPORT

Intern: 31 Application No  
PCT/GB 00/02513

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>US 3 968 219 A (RAHTZ DIETER ET AL)  6 July 1976 (1976-07-06)  cited in the application  claims 1,13,14</p> <p>-----</p>	1,2,11

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 00/02513

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
DE 2022712	A	25-11-1971	NONE	
US 3629282	A	21-12-1971	DE 1470148 A	04-06-1969
			FI 43993 B	30-04-1971
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			EP 0285730 A	12-10-1988
			JP 63267719 A	04-11-1988
US 4169147	A	25-09-1979	US 3957803 A	18-05-1976
			US 4036845 A	19-07-1977
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			FR 2296416 A	30-07-1976
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			JP 51091261 A	10-08-1976
			US 4139709 A	13-02-1979
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			AT 353261 B	12-11-1979
			AT 488077 A	15-04-1979
			AT 344689 B	10-08-1978
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			CH 617927 A	30-06-1980
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			CS 197253 B	30-04-1980
			CS 197252 B	30-04-1980
			DD 122533 A	12-10-1976
			DK 344375 A, B,	30-01-1976
			ES 439810 A	16-04-1977
			FR 2280374 A	27-02-1976
			GB 1519498 A	26-07-1978
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			IE 41639 B	13-02-1980
			IL 47768 A	31-10-1979
			JP 51036452 A	27-03-1976
			NL 7509060 A	02-02-1976
			SE 415252 B	22-09-1980
			SE 7508543 A	30-01-1976
			SU 593662 A	15-02-1978

## INTERNATIONAL SEARCH REPORT

Internat'l Application No

PCT/GB 00/02513

<b>A. CLASSIFICATION OF SUBJECT MATTER</b> IPC 7 C07D231/32 C07D231/30 A61K31/4152 A61P31/08 A61P37/06		
According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b> Minimum documentation searched (classification system followed by classification symbols) IPC 7 C07D A61K  Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched  Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, CHEM ABS Data		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	M. F. HUGHES ET AL.: MOLECULAR PHARMACOLOGY, vol. 34, no. 2, 1988, pages 186-93, XP000925977 page 186, summary; page 191, scheme 1; page 191-192	1,2,13, 14,16, 17,19, 21,22
X	P. S. PORTOGHESE ET AL.: BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 63, no. 3, 1975, pages 748-55, XP000925976 page 748 page 751 -page 752 page 754, figure 2  --- -/--	13,14, 17,20,22
<input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex.		
<b>* Special categories of cited documents:</b> "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "Z" document member of the same patent family		
Date of the actual completion of the international search  20 October 2000		Date of mailing of the international search report  06/11/2000
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer  Hass, C

## INTERNATIONAL SEARCH REPORT

Internat Application No

PCT/GB 00/02513

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	CHEMICAL ABSTRACTS, vol. 51, no. 14, 25 July 1957 (1957-07-25) Columbus, Ohio, US; abstract no. 10491d, column 10491; XP002150572 10491h, 10491i, 10492a, 10492b & K. M. HAMMOND ET AL.: J. CHEM. SOC., 1957, pages 1062-7, ---	13,14, 17,19
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# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

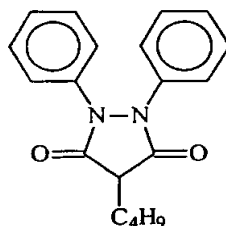
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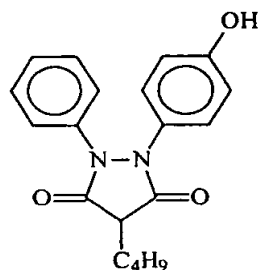
### Pyrazolidinol Compounds

The present invention relates to certain pyrazolidinols and their sulphur (i.e. thio/thiol) analogs and pharmaceutical compositions thereof for use in antiviral, e.g. anti-HIV therapy and as anti-inflammatories and immunomodulators.

Phenbutazone and oxyphenbutazone are 1,2-bis aromatic-3,5-pyrazolidinediones which have been used as non-steroidal anti-inflammatory drugs (NSAIDs)



Phenbutazone (PB)



Oxyphenbutazone (OPB)

Other 3,5-pyrazolidinediones have likewise been proposed for use as NSAIDs (see for example US-A-3968219 (Rahtz)) and the hydroxy-protected enol forms have been proposed as pro-drug forms of phenbutazone and oxyphenbutazone (see US-A-4117232 (Bodor), US-A-3957803 (Bodor), US-A-4169147 (Bodor), US-A-4036845 (Bodor) and US-A-4139709 (Bodor)).

In US-A-4956377 (Miesch) it was proposed that this class of NSAIDs had utility as an antiviral agent, in particular for the treatment of HIV.

We have now surprisingly found that where the 4-carbon of the N<sub>2</sub>C<sub>3</sub> ring carries an optionally protected

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hydroxy or thiol group, the compounds have very significantly enhanced antiviral, in particular anti-HIV, efficacy.

Thus viewed from one aspect the invention provides the use of an optionally hydroxy-protected 4-hydroxy or hydroperoxy-3,5-dioxo-pyrazolidine or an equivalent wherein a pyrazolidine ring attached oxygen is replaced by a sulphur, or a physiologically acceptable salt thereof, for the manufacture of a medicament for use in therapy or prophylaxis.

Where a particular 4-hydroxy or hydroperoxy-3,5-dioxo-pyrazolidine may exist in more than one stereoisomeric form, it may be used in single isomer form or as an isomer mixture, e.g. a racemic mixture.

Viewed from a further aspect, the invention provides an optionally hydroxy-protected 4-hydroxy or hydroperoxy-3,5-dioxo-pyrazolidine or an equivalent wherein a pyrazolidine ring attached oxygen is replaced by a sulphur, or a physiologically acceptable salt thereof.

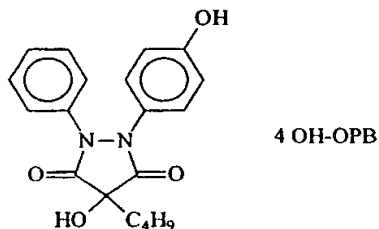
Viewed from a still further aspect the invention provides a method of treatment of the human or non-human (e.g. mammalian, reptilian or avian) body to combat an inflammatory or viral disease, preferably an immunodeficiency viral disease, in particular HIV, which method comprises administering to said body an optionally hydroxy-protected 4-hydroxy or hydroperoxy-3,5-dioxo-pyrazolidine or an equivalent wherein a pyrazolidine ring attached oxygen is replaced by a sulphur, or a physiologically acceptable salt thereof.

Viewed from a still further aspect, the invention provides a pharmaceutical composition comprising an optionally hydroxy-protected 4-hydroxy or hydroperoxy-3,5-dioxo-pyrazolidine or an equivalent wherein a pyrazolidine ring attached oxygen is replaced by a sulphur, or a physiologically acceptable salt thereof, together with at least one pharmaceutically acceptable

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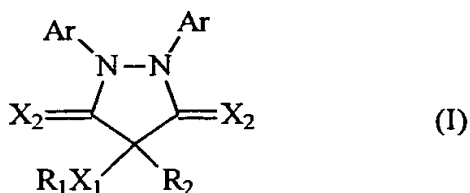
carrier or excipient.

The applicants have found that oxyphenbutazone, as commercially available, contains minute quantities of certain impurities, presumably as a result of undesired oxidative breakdown. One of these, present at about 0.4% wt, is 4-butyl-4-hydroxy-2(p-hydroxyphenyl)-1-phenyl-3,5-pyrazolidinedione (hereinafter "4-OH-OPB"), i.e.



4-OH-OPB is of course a compound according to the invention and thus it should be understood that references to the 4-hydroxy compounds of the invention, their use and compositions thereof should not be taken to include references to such compounds when in intimate admixture with overwhelmingly larger quantities of a 3,5-pyrazolidinedione which carries no optionally protected 4-hydroxy or 4-thiol group. By overwhelmingly larger is meant a relative weight ratio of at least 98:2. In general, the compounds of the invention should not desirably be used in intimate admixture with larger quantities (i.e. a relative weight ratio of more than 50:50) of such compounds carrying no O or S attached group at the 4-position, and more desirably they should not be used with such compounds present in greater than 10:90 weight ratio.

The compounds of the invention, hereinafter referred to as pyrazolidinols for convenience, will preferably be of formula I



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(where each  $X_2$ , which may be the same or different is O or S, preferably O;

$X_1$  is O, OO or S, preferably O or S, most preferably O;

$R_1$  is hydrogen or a hydroxyl or thiol protecting group (e.g. an acyl group, preferably containing up to 6 carbons, e.g. an acyl group such as an alkylcarbonyl group, for example acetyl), preferably hydrogen;

$R_2$  is hydrogen or more preferably a carbon attached organic group containing up to 10 carbons, e.g. an alkyl, alkenyl, alkynyl, alkaryl, aralkyl or aralkenyl group, optionally substituted, e.g. by a sulphonyl group; and

each Ar, which may be the same or different, is a homo or heterocyclic aromatic group, optionally substituted, e.g. by  $C_{1-6}$  alkyl or alkoxy groups) or a salt thereof.

In the compounds of the invention 0, 1 or 2 of the  $X_1$  and  $X_2$  groups may be S. It is thought that it is especially preferred that one thio  $X_2$  group be present.

In the compounds of the invention, the  $R_2$  group is preferably other than hydrogen and may for example be straight chain, branched, cyclic or cyclic-attached-to-straight chain. Preferably it is an alkyl or alkenyl group, especially a  $C_{1-6}$  alkyl or alkenyl group, e.g. n-propyl, n-butyl, n-pentyl or 1-methyl-but-2-en-4-yl or an aralkyl (e.g. benzyl) or alkaryl (e.g. methylphenyl) or arylsulphonylalkyl (eg phenylsulphonylethyl) group.

Where  $R_1$  in the compounds of the invention is other than hydrogen it is preferably a metabolically labile hydroxy- or thiol-protecting group which yields a physiologically tolerable  $R_1OH$  metabolite. Acyl groups are preferred in this regard.

In the compounds of formula I, where each  $X_2$  is oxygen and one Ar is phenyl, the other Ar is preferably other than phenyl e.g. parahydroxyphenyl.

A wide range of hydroxy- and thiol-protecting groups however is known from the literature (see McOmie, "Protective groups in organic chemistry", Plenum, 1973

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and Greene, "Protective groups in organic synthesis", Wiley Interscience, NY, 1981) and many compounds of formula I in which  $R_1$  is a protecting group may be useful as intermediates in the production of compounds of formula I in which  $R_1$  is hydrogen.

The Ar groups in the compounds of formula I are preferably 5 to 7 membered aromatic rings, optionally carrying a fused aromatic ring and optionally substituted on ring atoms, for example by  $C_{1-6}$  alkyl groups but especially by electron withdrawing substituents, e.g. hydroxy, thiol, phenyl,  $C_{1-6}$  alkoxy, cyano, halo (e.g. Cl, F, Br or I), protected hydroxy, or protected thiol. Ring heteroatoms will generally be selected from O, N and S, preferably with a single ring heteroatom in any aromatic Ar heterocycle. Ar is preferably phenyl optionally substituted, especially in the para-position by  $-X_1-R_1$  or Cl (where  $-X_1-R_1$  is as defined above). Especially preferably one Ar is phenyl and the other is p-hydroxy-phenyl.

Where the substitution of the pyrazolidinols of the invention is such that they may form addition salts with acids or bases, the addition salts which have physiologically tolerable counterions are of course preferred, e.g. sodium, organic amine, halides, phosphates, hydrogen carbonates, etc.

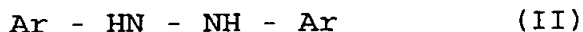
The pyrazolidinols of the invention may particularly advantageously be used in combination therapy with other antiviral, especially anti-HIV, agents, in particular reverse transcriptase inhibitors and/or protease inhibitors, e.g. zidovudine, didanosine, zalcitabine, stavudine, lamivudine, nevirapine, delavirdine, indinavir, ritonavir, nelfinavir, hydroxyurea, colchicine, AZT and 2',3'-dideoxyinosine (ddI). Such combination therapy forms a further aspect of the present invention.

A drawback of traditional combination therapy, has often been that even under intensive antiviral treatment with a combination of drugs, a little HIV production

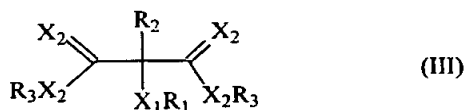
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continues and is unaffected by treatment. The compounds of the invention may prove to have an effect in reducing this residual HIV production when given in combination with other antiviral agents. This may be due to the increasing antiviral effect which has been seen in long term cell culture experiments and which may counteract any development of resistance to the compounds.

The pyrazolidinols of the invention may be prepared by oxidation of a corresponding compound where  $R_1X_1$  is replaced by hydrogen; by reaction of a corresponding compound where  $R_1X_1$  is  $HX_1$  with a hydroxy or thiol protecting agent to introduce a non-hydrogen  $R_1$  group; or by condensation of a hydrazine derivative with an optionally protected 2-hydroxy-propane dioic acid ester (or a sulphur analog), e.g. by condensation of a compound of formula II

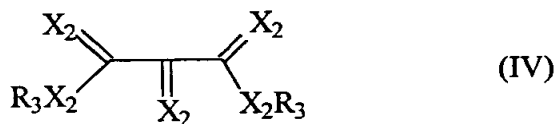


with a compound of formula III



where  $R_1$ ,  $R_2$ ,  $X_1$ ,  $X_2$  and Ar are as hereinbefore defined and  $X_2R_3$  is a leaving group, for example where  $R_3$  is an alkyl group, e.g. a  $C_{1-6}$  alkyl group.

Alternatively, a compound of formula II may be condensed with a compound of formula IV



(where  $X_2$  and  $R_3$  are as defined above) and then reacted with an alkylating agent, e.g.  $(R_2)_2\text{Zn}$  to produce a compound of formula I in which  $X_1R_1$  is OH or SH.

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For administration, the pyrazolidinols of the invention may be formulated in any convenient form, e.g. tablets, coated tablets (e.g. delayed release tablets), capsules, solutions, suspensions, dispersions, syrups, powders, sprays, suppositories, transdermal patches, gels, emulsions and creams. Administration may be via any convenient route, e.g. oral, rectal, transdermal, nasal, subcutaneous, intravenous, intramuscular, etc. Oral administration, e.g. of tablets or capsules is preferred. The pyrazolidinols may be formulated together with conventional pharmaceutical carriers, diluents or excipients, e.g. aqueous carriers (for example water for injections), binders, fillers, stabilizers, osmolality adjusting agents, effervescing agents, pH modifiers, viscosity modifiers, sweeteners, lubricants, emulsifiers, flavours, coating agents (e.g. gastric juice resistant coatings), etc. Where any formulation results in a loss of compound, this loss should be calculated and the dosage increased proportionally to obtain the desired active concentration.

The dosage of the pyrazolidinols given according to the invention will depend on the size and species of the subject being treated but will generally be in the range of 0.05 to 2000 mg/day, more particularly 0.5 to 1000 mg/day, especially 1 to 100 mg/day, preferably with administration being effected once, twice, three times or four times daily. For mice, doses of up to 2000 mg/kg (corresponding to 20 mM maximal concentration in extracellular fluid) could be given before lethal dosage was reached, ie effective treatment doses were up to 200000 times smaller than the lethal dose.

For regular, e.g. continuous daily treatment according to the invention, the daily dosage of the pyrazolidinol will preferably be in the range 5 nmol to 2  $\mu$ mol/kg bodyweight, more preferably 100 nmol to 1.5  $\mu$ mol/kg, especially 500 nmol to 1  $\mu$ mol/kg.

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Inhibition of virus production may be achieved by small intermittent doses of pyrazolidinol, and are expected to induce inhibition of the virus after a latency of about 11 weeks. Subsequently, inhibition may be expected to level out, should resistance to the compound develop. Such doses may be administered at a frequency of 1-14 days, preferably 7 days. The doses should be equivalent to a concentration in plasma/tissue fluid of from 100-1000 nM and may be obtained by ingestion or injection of from 0.7-7 mg in a 70 Kg human.

However, in a particularly preferred embodiment of the invention, a pyrazolidinol according to the invention is administered at a dose sufficient to suppress T-lymphocyte (CD4 and CD8 cell) growth (e.g. a daily dose of 0.1 to 10  $\mu$ mol/kg) for a period of 1 to 14 days, preferably 2 to 7 days at intervals of at least 3 months, preferably at least 9 months, e.g. 10 to 18 months. In this way the patient's immune system may be "refreshed" by removal of the preponderance of T-lymphocytes directed to HIV antigens. Such a treatment indeed is novel and forms a further aspect of the invention. Viewed from this aspect the invention provides a method of combatting HIV infection which comprises administering to an HIV-infected patient a T-lymphocyte growth suppressing agent, e.g. a pyrazolidinol, in an amount sufficient to suppress T-lymphocyte growth in said patient for a period sufficient to reduce the T-lymphocyte concentration in the lymphatic system, e.g. the lymph nodes, in said patient by at least 25%, more preferably at least 50%, said administration being repeated at intervals of at least 3 months, preferably at least 9 months.

High tissue concentrations intended to give an immunomodulating effect should preferably be given for limited periods at doses of 1 $\mu$ M or above in plasma/tissue fluid. Such doses and lengths of

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administration will vary according to the condition of each patient and may be decided with the guidance of tests such as the count of HIV memory subsets of T8 and T4. As stated above, the goal of treatment according to this aspect of the invention should be to reduce subsets which are found to be too prevalent without overly affecting naive T-cells.

In order to obtain the desired reduction of HIV specific lymphocytes (e.g. HIV memory CD8 and CD4 lymphocytes) without overly affecting naive T-lymphocytes or other essential blood cells, monoclonal antibodies against the unwanted subtypes may also be administered. Further, drugs such as kolchicine and/or hydroxy-urea may be included in the intermittent intensive treatment. Such additional drugs are anticipated to have a somewhat different immunomodulating effect to the compounds of the invention and so may be used advantageously in combination with pyrazolidinols for refreshing the immune system.

Besides HIV, the pyrazolidinols of the invention may be used to combat other viral infections, especially retroviral infections but also infections by togaviridea, reoviridea, picornaviridea, hantaviridea, orthomyxoviridea, paramyxoviridea, mononegaviralis, viral hepatitis, haemorrhagic fevers, flaviviridea, viral encephalitis, coronaviridea, calciviridea, adenoviridea, papovaviridea, arboviridea, pox virus, rhabdoviridea, herpes virus and arenaviridea. The pyrazolidinols of the invention may in particular be used to combat viral infections of CD4 cells, e.g. HIV-1, HIV-2, HTLV-I, HTLV-II and herpes viruses, for example to combat AIDS, T-cell tumours (e.g. Sezary Syndrome, mycosis fungoides and T-cell lymphoma, and particularly CD4 cell tumours), tropic spastic paraparesis, and Kaposi's sarcoma. Moreover despite not being of the accepted formula for NSAIDs (which

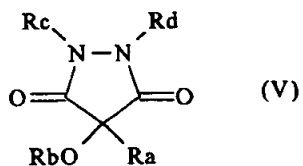
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would require an acid proton in place of  $R_1X_1$  at the 4-position), they may be used as anti-inflammatory drugs. All these uses form aspects of the invention.

Due to the immunomodulating effect of the compounds of the invention, they are expected to have uses in control of other immune-system related diseases, such as auto immune diseases and as immunosuppressants. In particular, the compounds of the invention are expected to have a positive effect on the generation of autoimmune diseases, on developed autoimmune diseases and on diseases related to such diseases, such as Addison's disease, Behçet's syndrome, diabetes mellitus and other endocrine diseases, haemolytic anaemia, lupus erythematosus, multiple sclerosis, myasthenia gravis, pernicious anaemia, polyglandular deficiency, polymyositis, dermatomyositis, testicular failure, thrombocytopenic purpura, Crohns disease, ulcerative colitis, rheumatic disorders (e.g. rheumatoid arthritis) etc.

The effect of the compounds of the invention on the immune system may also be that of immunosuppression. Such an effect may be used, for example, to control rejection of a medical transplant or implant. In particular, the compounds may be used to reduce rejection following tissue or organ transplant.

Various 4-hydroxy-3,5-dioxo-pyrazolidines are known in the literature (although not for medical purposes such as HIV therapy). These are compounds of formula V



where  $R_a$  to  $R_d$  are as set out in Table 1 below:

Table 1

$R_a$	$R_b$	$R_c$	$R_d$
H	H	H	$C_6H_5$
H	H	$C_6H_5$	$C_6H_5$
$CH_3$	H	H	$C_6H_5$
$CH_3$	H	H	$-CH_2-C_6H_5$
$CH_3$	H	H	$p-CH_3O-C_6H_4$
$CH_3$	H	H	$p-Cl-C_6H_4$
$C_2H_5$	H	H	$C_6H_5$
$C_2H_5$	H	$C_6H_5$	$C_6H_5$
$C_2H_5$	H	H	N-methyl-piperidin-4-yl
$iC_3H_7$	H	H	$C_6H_5$
$nC_3H_7$	H	H	$C_6H_5$
$nC_3H_7$	H	$C_6H_5$	$C_6H_5$
$nC_3H_7$	H	H	5-phenyl-triazol-1-yl
$C_4H_9$	H	H	$C_6H_5$
$C_4H_9$	H	$C_6H_5$	$C_6H_5$
$C_4H_9$	H	$C_6H_5$	$p-OH-C_6H_4$
$C_4H_9$	OH	$C_6H_5$	$C_6H_5$
$C_4H_9$	OH	$C_6H_5$	$p-OH-C_6H_4$
$C_4H_9$	H	H	N-methyl-piperidin-4-yl
$C_5H_{11}$	H	H	$C_6H_5$
$C_5H_{11}$	H	$C_6H_5$	$C_6H_5$
$C_5H_{11}$	H	H	5-phenyl-triazol-1-yl
Cyclohexyl	H	H	$C_6H_5$
Phenyl	H	H	$C_6H_5$
Phenyl	H	$C_6H_5$	$C_6H_5$
Benzyl	H	H	$C_6H_5$
Benzyl	H	$C_6H_5$	$C_6H_5$
$CH_3CO(CH_2)_2$	H	$C_6H_5$	$C_6H_5$
$(CH_3)_2C=CH-$	H	$C_6H_5$	$C_6H_5$
$(CH_2)_2C=CHCH_2$	H	$C_6H_5$	$C_6H_5$
$C_6H_5SCH_2CH_2$	H	$C_6H_5$	$C_6H_5$
Pyrrolidin-1-yl	H	$C_6H_5$	$C_6H_5$
Piperidin-1-yl	H	$C_6H_5$	$C_6H_5$
Morpholin-4-yl	H	$C_6H_5$	$C_6H_5$

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Such compounds are thus not claimed per se herein; however their use and pharmaceutical compositions containing them do form part of the scope of the invention.

The invention will now be illustrated further by the following non-limiting Examples and by reference to the Figures, in which:

Figure 1 shows the HIV antigen concentration in human CD4 cells infected with HIV and treated with 4-butyl-4-hydroxy-2(p-hydroxyphenyl)-1-phenyl-3,5-pyrazolidinedione (4OH-OPB) or phenbutazone (PB) at various concentrations;

Figure 2 shows the effect of 4-butyl-4-hydroxy-2(p-hydroxyphenyl)-1-phenyl-3,5-pyrazolidinedione (4OH-OPB) when used in combination with AZT;

Figure 3 shows the effect of 4-butyl-4-hydroxy-2(p-hydroxyphenyl)-1-phenyl-3,5-pyrazolidinedione (4OH-OPB) when used in combination with indinavir; and;

Figure 4 shows the effect of 4-butyl-4-hydroxy-2(p-hydroxyphenyl)-1-phenyl-3,5-pyrazolidinedione (4OH-OPB) when used in combination with nevirapine;

A similar effect to those shown in figures 2-4 is seen when OPB is used in combination with 2',3'-dideoxyinosine (ddI).

#### **EXAMPLE 1**

##### **Preparation of 4-Methoxyazobenzene**

A mixture of 4-phenylazophenol (9.9g; 50 mmol), iodomethane (7.1 g; 50 mmol), potassium carbonate (6.9 g; 50 mmol), and acetone (100 ml) was refluxed 48 h. After evaporating off the solvent, the residue was dissolved in water (25 ml), diethyl ether (50 ml) and THF (30 ml). The aqueous layer was extracted with ether (3 × 20 ml) and the combined organic solutions were washed with saturated NaCl solution (1 × 20 ml) and

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dried ( $\text{MgSO}_4$ ). After filtration and evaporation, the residue was recrystallized from 96% ethanol to give 8.7 g (82%).

#### EXAMPLE 2

##### Preparation of 1-(4-Methoxyphenyl)-2-phenylhydrazine

Zinc powder (10.0 g; 0.15 mol) was added to a stirred mixture of 4-methoxyazobenzene (4.24 g; 20.0 mmol) in 96% ethanol (75 ml) and saturated  $\text{NH}_4\text{Cl}$  solution (2.0 ml) at 0 °C (bath temperature). Two more portions of saturated  $\text{NH}_4\text{Cl}$  solution (2.0 ml) were added at 1.5 h intervals. The yellowish solution was poured into cold water (100 ml) and filtered. The residue was extracted with methylene chloride (5 × 50 ml). The combined aqueous phases were extracted with methylene chloride (3 × 25 ml). The combined organic solutions were dried ( $\text{Na}_2\text{SO}_4$ ), filtered, and evaporated to give 4.3 g crude 1-(4-methoxyphenyl)-2-phenylhydrazine as a reddish oil.

#### EXAMPLE 3

##### Preparation of 4-(1-Butyl)-1-(4-methoxyphenyl)-2-phenyl-3,5-pyrazolidinedione

Diethyl butylmalonate (4.33 g; 20.0 mmol) was added to a stirred solution of sodium (0.46 g; 20.0 mmol) in absolute ethanol (20 ml), followed by crude 1-(4-methoxyphenyl)-2-phenylhydrazine (4.3 g; 20 mmol max.) in absolute ethanol (5 ml). About 2/3 of the ethanol was distilled off and xylene (20 ml) was added to the residue. The reaction mixture was heated to 140-145 °C (bath temperature) for 15 h to distill off the rest of the ethanol. The reaction mixture was cooled to 0 °C (bath temperature) and poured into ice water (ca. 100 ml). The aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  (2 × 15

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ml); the extracts were discarded. The cold aqueous layer was acidified with 6 M HCl (5 ml) and extracted with  $\text{CH}_2\text{Cl}_2$  ( $3 \times 10$  ml). The combined extracts were washed with water ( $2 \times 10$  ml) and dried ( $\text{MgSO}_4$ ). Filtration and evaporation gave 3.84 g amber oil. Purified by flash chromatography on a  $130 \times 65$  mm silica gel 60 column eluted with ethyl acetate-heptane (1:3) to give 1.45 g (21%) colourless oil.

$^1\text{H}$  NMR (200 MHz;  $\text{CDCl}_3$ ):  $\delta$  0.90 (3H, t,  $J = 7.5$  Hz), 1.25-1.6 (4H, m), 2.0-2.15 (2H, m), 3.37 (3H, t,  $J = 6.0$  Hz), 3.69 (3H, s), 6.81 (2H, d,  $J = 8.4$  Hz), 7.22 (2H, d,  $J = 8.6$  Hz), 7.1-7.35 (5H, m).

$^{13}\text{C}$  NMR (50 MHz;  $\text{CDCl}_3$ ):  $\delta$  13.6, 22.2, 27.5, 27.6, 45.6, 54.7, 112.9, 121.6, 123.3, 125.4, 127.1, 127.4, 133.9, 156.5, 168.2, 168.7.

#### **EXAMPLE 4**

##### **Preparation of 1,2-Diphenyl-4-(4-methylphenyl)-3,5-pyrazolidinedione**

Prepared from 1,2-diphenylhydrazine (3.70 g; 20.0 mmol), diethyl 2-(p-tolyl)malonate (5.0 g; 20.0 mmol), and sodium (0.46 g; 20.0 mmol) using the procedure of Example 3. The crude product crystallized on standing and was recrystallized twice from absolute ethanol to give 1.22 g (18%), mp 184-185 °C.

$^1\text{H}$  NMR (200 MHz;  $\text{CDCl}_3$ ):  $\delta$  2.31 (3H, s), 4.51 (1H, s), 7.1-7.4 (14H, m).

$^{13}\text{C}$  NMR (50 MHz;  $\text{CDCl}_3$ ):  $\delta$  21.1, 51.9, 122.7, 126.9, 128.3, 129.0, 129.9, 135.8, 138.3, 168.6.

#### **EXAMPLE 5**

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**Preparation of 4-Benzyl-1,2-diphenyl-3,5-pyrazolidinedione**

Prepared from 1,2-diphenylhydrazine (4.60 g; 25.0 mmol), diethyl benzylmalonate (5.0 g; 20 mmol), and sodium (0.46 g; 20.0 mmol) using the procedure of Example 3. The crude product was recrystallized from absolute ethanol to give 3.51 g (50%), mp 136-137 °C [lit. 137-138 °C (Beil. III/IV, **24**, 1463)].

<sup>1</sup>H NMR (200 MHz; CDCl<sub>3</sub>): δ 3.41 (2H, d, J = 4.6 Hz), 3.63 (1H, t, J = 5.0 Hz), 6.85-7.3 (10H, m).

<sup>13</sup>C NMR (50 MHz; CDCl<sub>3</sub>): δ 33.9, 48.5, 123.2, 126.9, 127.3, 128.6, 128.7, 129.9, 135.2, 135.4, 169.3.

**EXAMPLE 6**

**Preparation of 4-Allyl-1,2-diphenyl-3,5-pyrazolidinedione**

Prepared from 1,2-diphenylhydrazine (5.2 g; 28.0 mmol), diethyl allylmalonate (5.0 g; 25.0 mmol), and sodium (0.58 g; 25.0 mmol) using the procedure of Example 3. The crude product was recrystallized from absolute ethanol to give 2.21 g (30%) tan crystals, mp 135-137 °C.

<sup>1</sup>H NMR (200 MHz; CDCl<sub>3</sub>): δ 2.82 (2H, t, J = 6.0 Hz), 3.46 (2H, t, J = 5.4 Hz), 5.1-5.3 (2H, dd), 5.7-5.95 (1H, m), 7.1-7.3 (10H, m).

<sup>13</sup>C NMR (50 MHz; CDCl<sub>3</sub>): δ 31.7, 46.4, 119.9, 122.7, 126.8, 128.9, 131.7, 135.6, 169.5.

**EXAMPLE 7**

**Preparation of 4-(1-Butyl)-4-hydroxy-1-(4-hydroxyphenyl)-2-phenyl-3,5-pyrazolidinedione (4OH-OPB)**

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**Method A**

Oxyphenbutazone.H<sub>2</sub>O (1 mmol), 30% H<sub>2</sub>O<sub>2</sub> (0.7 mL), 1N NaOH (0.1 mL) and methanol (3.5 mL) are allowed to stand for 13 hours at ambient temperature. The mixture is then poured into 5% HCl (20 mL) and extracted with ethyl acetate (2 x 20 mL). The ethyl acetate phase is separated, dried over sodium carbonate and the solvent is removed under reduced pressure without heating. The residue is subjected to flash chromatography (silica/ethyl acetate). The title product is recrystallized from ethyl acetate.

**Method B**

A solution of oxyphenbutazone hydrate (2.0 g; 5.8 mmol), 35% hydrogen peroxide solution (3.4 ml; 40 mmol), and 1 M sodium hydroxide solution (0.6 ml; 0.6 mmol) in methanol (20 ml) was allowed to stand for 24 h at ambient temperature. The mixture was acidified with 1 M HCl solution (50 ml) and extracted with ethyl acetate (4 x 15 ml). The combined extracts were washed with saturated NaCl solution (1 x 10 ml) and dried (MgSO<sub>4</sub>). After filtration and evaporation, the residue was purified by flash chromatography on a 100 x 65 mm silica gel 60 column eluted with ethyl acetate-heptane (1:1), taking 50-ml fractions, giving 1.3 g (66%).

<sup>1</sup>H NMR (200 MHz; CDCl<sub>3</sub>): δ 0.88 (3H, t, *J* = 6.6 Hz), 1.25-1.5 (4H, m), 1.95-2.05 (2H, m), 6.49 (1H, br s), 6.75 (2H, d, *J* = 8.9 Hz), 7.12 (2H, d, *J* = 8.9 Hz), 7.1-7.35 (5H, m).

<sup>13</sup>C NMR (50 MHz; CDCl<sub>3</sub>): δ 13.6, 22.3, 24.3, 36.2, 72.8, 114.3, 121.9, 123.8, 125.3, 125.7, 127.2, 133.5, 154.6, 169.0, 169.5.

**EXAMPLE 8****Preparation of 4-(1-Butyl)-4-hydroxy-1-(4-**

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**methoxyphenyl)-2-phenyl-3,5-pyrazolidinedione**

Prepared from 4-(1-butyl)-1-(4-methoxyphenyl)-2-phenyl-3,5-pyrazolidinedione (1.35 g; 3.8 mmol), 35% H<sub>2</sub>O<sub>2</sub> (4.3 ml; 50 mmol), 2 M NaOH (0.35 ml; 0.7 mmol), and methanol (50 ml) using the procedure of Example 7. Purified by flash chromatography on a 110 × 65 mm silica gel 60 column eluted with ethyl acetate-heptane (1:1) to give 0.7 g (52%).

<sup>1</sup>H NMR (200 MHz; CDCl<sub>3</sub>): δ 0.85 (3H, t, J = 6.2 Hz), 1.2-1.5 (4H, m), 2.0-2.1 (2H, m), 3.69 (3H, s), 4.8 (1H, br s), 6.77 (2H, d, J = 9.0 Hz), 7.19 (2H, d, J = 9.0 Hz), 7.1-7.35 (5H, m).

<sup>13</sup>C NMR (50 MHz; CDCl<sub>3</sub>): δ 13.5, 22.3, 24.3, 36.7, 54.7, 73.3, 113.0, 122.1, 123.8, 125.8, 126.1, 127.5, 133.0, 156.7, 168.5, 169.0.

**EXAMPLE 9****Preparation of 1,2-Diphenyl-4-hydroxy-4-[2-(phenylsulfonyl)ethyl]-3,5-pyrazolidinedione**

Prepared from (±)-sulfinpyrazone (2.02 g; 5.0 mmol), 35% H<sub>2</sub>O<sub>2</sub> (4.3 ml; 50 mmol), 2 M NaOH (0.35 ml; 0.7 mmol), and methanol (50 ml) using the procedure of Example 7. Purified by flash chromatography on a 130 × 65 mm silica gel 60 column eluted with ethyl acetate-acetic acid (20:1) to give 80 mg (4%).

<sup>1</sup>H NMR (200 MHz; CDCl<sub>3</sub>): δ 2.1-2.5 (2H, m), 3.0-3.7 (2H, m), 5.5 (1H, br s), 6.4-7.9 (15H, m).

<sup>13</sup>C NMR (50 MHz; CDCl<sub>3</sub>): δ 28.7, 47.5, 70.2, 121.5, 122.9, 125.8, 126.5, 127.4, 127.7, 127.9, 129.9, 133.3, 133.4, 136.9, 139.2, 167.5, 168.0.

**EXAMPLE 10****1,2-Diphenyl-4-hydroxy-4-(4-methylphenyl)-3,5-**

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**pyrazolidinedione**

A mixture of 1,2-diphenyl-4-(4-methylphenyl)-3,5-pyrazolidinedione (1.10 g; 3.2 mmol), 35% H<sub>2</sub>O<sub>2</sub> (0.47 ml; 5.5 mmol), and acetic acid (40 ml) was stirred 16 days at room temperature. Sodium metabisulfite (1.0 g) was added and excess acetic acid evaporated off. The residue was dissolved in hot ethyl acetate (25 ml) and benzene (25 ml) and filtered. After cooling to room temperature, the mixture was filtered and the residue recrystallized from 50% aqueous ethanol (20 ml) to give 0.58 g (53%).  
<sup>1</sup>H NMR (200 MHz; CDCl<sub>3</sub>): δ 2.32 (3H, s), 7.0-7.45 (14H, m).

<sup>13</sup>C NMR (50 MHz; CDCl<sub>3</sub>): δ 21.1, 57.9, 123.9, 124.5, 127.0, 128.3, 128.4, 128.7, 130.4, 135.6, 139.0, 168.5.

**EXAMPLE 11****Preparation of 4-Benzyl-1,2-diphenyl-4-hydroxy-3,5-pyrazolidinedione**

Prepared from 4-benzyl-1,2-diphenyl-3,5-pyrazolidinedione (3.3 g; 9.6 mmol), 35% H<sub>2</sub>O<sub>2</sub> (1.4 ml; 16.3 mmol), and acetic acid (50 ml) using the procedure of Example 10 to give 1.0 g (30%).

<sup>1</sup>H NMR (200 MHz; CDCl<sub>3</sub>): δ 3.30 (2H, s), 6.75-7.3 (15H, m).

<sup>13</sup>C NMR (50 MHz; CDCl<sub>3</sub>): δ 43.1, 75.4, 123.0, 126.7, 127.5, 128.4,, 130.2, 132.1, 134.7, 170.1.

**EXAMPLE 12****Antiviral activity of 4OH-OPB (Example 7)**

4OH-OPB was added to cultures of growing MT4 cells (a

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human CD4 cell line). HIV-1, stored in the culture medium at  $-75^{\circ}\text{C}$  was thawed and added in an amount which infected about 1 in 7 cells in each culture. The virus was absorbed to the cells for 2.3 hours at ambient temperature whereafter the cultures were centrifuged at 1200 rpm, the medium was removed, the cells were suspended in fresh growth medium and 4OH-OPB was added to concentrations of 1, 10 and 100  $\mu\text{M}$  (diluted in medium from a stock solution of 20 mM in DMSO). After 72 hours the HIV antigen concentration was determined using Abbott's test. By way of comparison phenbutazone (PB) was tested analogously. The results are shown in Figure 1 and demonstrate inhibition of virus production by 4OH-OPB at concentrations above the lowest tested.

### EXAMPLE 13

#### Combination Antiviral effect with 4OH-OPB

Cell culture experiments were carried out as in Example 12, but in place of 4OH-OPB (0-100  $\mu\text{M}$ ) was added:

- i) 4OH-OPB (0-10  $\mu\text{M}$ ) with AZT (0-1  $\mu\text{M}$ )
- ii) 4OH-OPB (0-100  $\mu\text{M}$ ) with Indinavir (0-100  $\mu\text{M}$ )
- iii) 4OH-OPB (0-100  $\mu\text{M}$ ) with Nevirapin (0-10  $\mu\text{M}$ )
- iv) 4OH-OPB (0-10  $\mu\text{M}$ ) with ddI (0-100  $\mu\text{M}$ )

The results are shown in Figures 2-5 respectively and demonstrate the enhanced anti-HIV effect of 4OH-OPB in combination with other anti-viral agents.

### EXAMPLE 14

#### Preparation of capsules for oral use

4-OH OPB (Example 7)	50 mg
Amylum maydis	q.s.

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The powder is mixed and filled into hard gelatin capsules (Capsugel size 00).

#### EXAMPLE 15

##### Preparation of tablets

	Gram
4-OH OPB (Example 7)	200
Lactose	85
Polyvinylpyrrolidone	5
Starch	42
Talcum powder	15
Magnesium stearate	3

4-OH OPB and lactose are screened through a 0.15 mm sieve and mixed together with an aqueous solution of polyvinyl-pyrrolidone. The mass is granulated, and the dried (40°C) granulate is mixed with starch, talcum powder and magnesium stearate. The granulate is compressed into tablets. The tablet diameter is 11 mm, the tablet weight is 350 mg and each tablet contains 200 mg 4-OH OPB.

#### EXAMPLE 16

##### Preparation of a suspension for rectal administration

Methyl p-hydroxybenzoate (70 mg) and propyl-p-hydroxybenzoate (15 mg) are dissolved in water (100 ml) at 90°C. After cooling to 30°C, methyl cellulose (2g) is added and the mixture is agitated for 3 hours. 1 gram 4-OH OPB (Example 7) is screened through a 0.15 mm sieve, and dispersed in the solution under vigorous stirring. The suspension is filled in a 100 ml tube. The suspension contains 10 mg 4-OH OPB/ml.

**EXAMPLE 17****Preparation of oral suspension**

	Gram
4OH OPB (Example 7)	10
Carboxymethyl cellulose	1.5
Sorbitol	200
Sodium benzoate	1.0
Orange essence	0.3
Apricot essence	0.7
Ethanol	50
Water	236.5

Carboxymethyl cellulose, sorbitol and sodium benzoate are dissolved in water with stirring for 2 hours. A solution of the essences in ethanol is added. 4-OH OPB is screened through a 0.15 mm sieve and dispersed in the solution under vigorous stirring. The suspension (10 gram) is filled in a 20 ml tube. Each tube contains 200 mg 4-OH OPB.

**EXAMPLE 18****Mouse toxicity**

20g mice were given single doses of 4OH-OPB (20 mM in DMSO) intraperitoneally. Doses of 1 to 100  $\mu$ M (in ECF), corresponding to 0.29 to 29  $\mu$ M/kg bodyweight, produced no toxic effect. Furthermore, injection of 4OH-OPB could be increased to 2000 mg/kg (corresponding to 20 mM in the extracellular fluid) before the mice started to die (6 out of 10 died at 2000 mg/kg). Thus the concentrations that effectively inhibit HIV replication in cell cultures are up to 200000 times lower than the lethal dose in mice.

Claims

1. The use of an optionally hydroxy-protected 4-hydroxy or hydroperoxy-3,5-dioxo-pyrazolidine or an equivalent wherein a pyrazolidine ring attached oxygen is replaced by a sulphur, or a physiologically acceptable salt thereof, for the manufacture of a medicament for use in therapy or prophylaxis.
2. A method of treatment of the human or non-human body to combat an inflammatory or viral disease, which method comprises administering to said body an optionally hydroxy-protected 4-hydroxy or hydroperoxy-3,5-dioxo-pyrazolidine or an equivalent wherein a pyrazolidine ring attached oxygen is replaced by a sulphur, or a physiologically acceptable salt thereof.
3. A method as claimed in claim 2 comprising administering said optionally hydroxy-protected 4-hydroxy or hydroperoxy-3,5-dioxo-pyrazolidine or an equivalent wherein a pyrazolidine ring attached oxygen is replaced by a sulphur, or a physiologically acceptable salt thereof in combination with another antiviral agent.
4. A method as claimed in claim 3 wherein said additional antiviral agent is at least one antiviral agent selected from a reverse transcriptase inhibitor and a protease inhibitor.
5. A method as claimed in claim 3 wherein said additional antiviral agent is an agent selected from the group of AZT, indinavir, nevirapine and 2',3'-dideoxyinosine (ddI).
6. A method as claimed in any of claims 2 to 5 wherein said disease is a disease caused by a pathogen from the

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group of togaviridea, reoviridea, picornaviridea, hantaviridea, orthomyxoviridea, paramyxoviridea, mononegaviralis, viral hepatitis, haemorrhagic fevers, flaviviridea, viral encephalitis, coronaviridea, calciviridea, adenoviridea, papovaviridea, arboviridea, pox virus, rhabdoviridea, arenaviridea HIV-1, HIV-2, HTLV-I, HTLV-II and herpes viruses.

7. A method of combatting HIV infection which comprises administering to an HIV-infected patient a T-lymphocyte growth suppressing agent in an amount sufficient to suppress T-lymphocyte growth in said patient for a period sufficient to reduce the T-lymphocyte concentration in the lymphatic system in said patient by at least 25% said administration being repeated at intervals of at least 3 months.

8. A method of combatting HIV infection as claimed in claim 6 wherein said T-lymphocyte growth suppressing agent is a pyrazolidinol.

9. A method as claimed in claim 7 or claim 8 wherein said interval is at least 9 months.

10. A method as claimed in any of claims 7 to 9 wherein a 4-hydroxy or hydroperoxy-3,5-dioxo-pyrazolidine or an equivalent wherein a pyrazolidine ring attached oxygen is replaced by a sulphur, or a physiologically acceptable salt thereof is administered in a daily dose of 0.1 to 10  $\mu\text{mol/kg}$  bodyweight.

11. A pharmaceutical composition comprising an optionally hydroxy-protected 4-hydroxy or hydroperoxy-3,5-dioxo-pyrazolidine or an equivalent wherein a pyrazolidine ring attached oxygen is replaced by a sulphur, or a physiologically acceptable salt thereof, together with at least one pharmaceutically acceptable

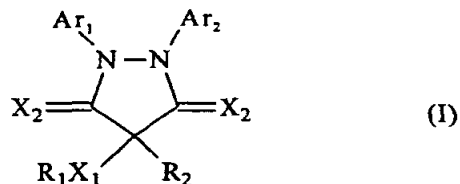
- 24 -

carrier or excipient.

12. A pharmaceutical composition as claimed in claim 11 additionally comprising another antiviral agent.

13. An optionally hydroxy-protected 4-hydroxy or hydroperoxy-3,5-dioxo-pyrazolidine or an equivalent wherein a pyrazolidine ring attached oxygen is replaced by a sulphur, or a physiologically acceptable salt thereof.

14. A compound of formula I



(where each  $X_2$ , which may be the same or different is O or S,

$X_1$  is O, OO or S,

$R_1$  is hydrogen or a hydroxyl or thiol protecting group,

$R_2$  is hydrogen or a carbon attached organic group containing up to 10 carbons, and each of

$Ar_1$  and  $Ar_2$ , which may be the same or different, is a homo or heterocyclic aromatic group) or a salt thereof.

15. A compound of claim 14 wherein  $R_1$ ,  $R_2$ ,  $X_1$ ,  $X_2$ ,  $Ar_1$  and  $Ar_2$  are as defined in claim 14, providing that if  $X_1$  and each  $X_2$  is O, the remaining groups do not correspond to the following table:

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$R_2$	$R_1$	$Ar_1$	$Ar_2$
H	H	H	$C_6H_5$
H	H	$C_6H_5$	$C_6H_5$
$CH_3$	H	H	$C_6H_5$
$CH_3$	H	H	$-CH_2-C_6H_5$
$CH_3$	H	H	$p-CH_3O-C_6H_4$
$CH_3$	H	H	$p-Cl-C_6H_4$
$C_2H_5$	H	H	$C_6H_5$
$C_2H_5$	H	$C_6H_5$	$C_6H_5$
$C_2H_5$	H	H	N-methyl-piperidin-4-yl
$iC_3H_7$	H	H	$C_6H_5$
$nC_3H_7$	H	H	$C_6H_5$
$nC_3H_7$	H	$C_6H_5$	$C_6H_5$
$nC_3H_7$	H	H	5-phenyl-triazol-1-yl
$C_4H_9$	H	H	$C_6H_5$
$C_4H_9$	H	$C_6H_5$	$C_6H_5$
$C_4H_9$	H	$C_6H_5$	$p-OH-C_6H_4$
$C_4H_9$	OH	$C_6H_5$	$C_6H_5$
$C_4H_9$	OH	$C_6H_5$	$p-OH-C_6H_4$
$C_4H_9$	H	H	N-methyl-piperidin-4-yl
$C_5H_{11}$	H	H	$C_6H_5$
$C_5H_{11}$	H	$C_6H_5$	$C_6H_5$
$C_5H_{11}$	H	H	5-phenyl-triazol-1-yl
Cyclohexyl	H	H	$C_6H_5$
Phenyl	H	H	$C_6H_5$
Phenyl	H	$C_6H_5$	$C_6H_5$
Benzyl	H	H	$C_6H_5$
Benzyl	H	$C_6H_5$	$C_6H_5$
$CH_3CO(CH_2)_2$	H	$C_6H_5$	$C_6H_5$
$(CH_3)_2C=CH-$	H	$C_6H_5$	$C_6H_5$
$(CH_2)_2C=CHCH_2$	H	$C_6H_5$	$C_6H_5$
$C_6H_5SCH_2CH_2$	H	$C_6H_5$	$C_6H_5$
Pyrrolidin-1-yl	H	$C_6H_5$	$C_6H_5$
Piperidin-1-yl	H	$C_6H_5$	$C_6H_5$
Morpholin-4-yl	H	$C_6H_5$	$C_6H_5$

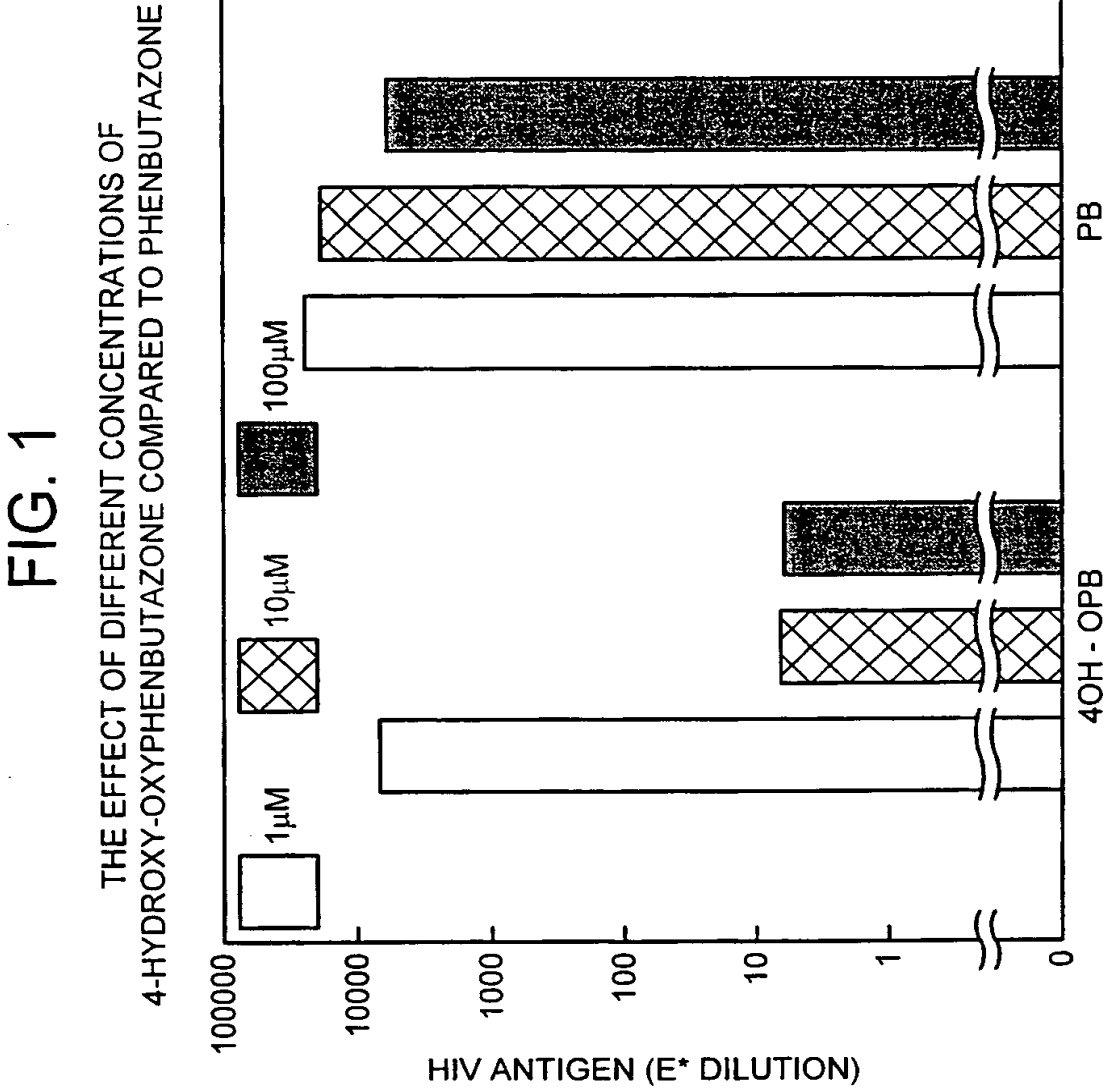
- 26 -

16. A compound as claimed in claim 14 or claim 15 wherein one  $X_2$  group is S.
17. A compound as claimed in any of claims 14 to 16 wherein  $X_1$  is O.
18. A compound as claimed in any of claims 14 to 17 wherein  $R_1$  is acyl.
19. A compound as claimed in any of claims 14 to 18 wherein  $R_1$  is hydrogen.
20. A compound as claimed in any of claims 14 to 19 wherein one of  $Ar_1$  and  $Ar_2$  is Ph and the other is 4-hydroxyphenyl.
21. A compound as claimed in claim 14 wherein each  $X_2$  is oxygen,  $R_1X_1$  is HO or  $CH_3CO.O$ , each of  $Ar_1$  and  $Ar_2$ , which may be the same or different is optionally halo or hydroxy substituted phenyl, and  $R_2$  is  $C_{1-6}$  alkyl or alkenyl, or a salt thereof.
22. A compound as claimed in any of claims 14 to 21 for use as a medicament.
23. 4-Butyl-4-hydroxy-2(p-hydroxyphenyl)-1-phenyl-3,5-pyrazolidinedione for use as a medicament.
24. A method of treatment of the human or non-human body to combat an autoimmune disease or tissue rejection, which method comprises administering to said body an optionally hydroxy-protected 4-hydroxy or hydroperoxy-3,5-dioxo-pyrazolidine or an equivalent wherein a pyrazolidine ring attached oxygen is replaced by a sulphur, or a physiologically acceptable salt thereof.

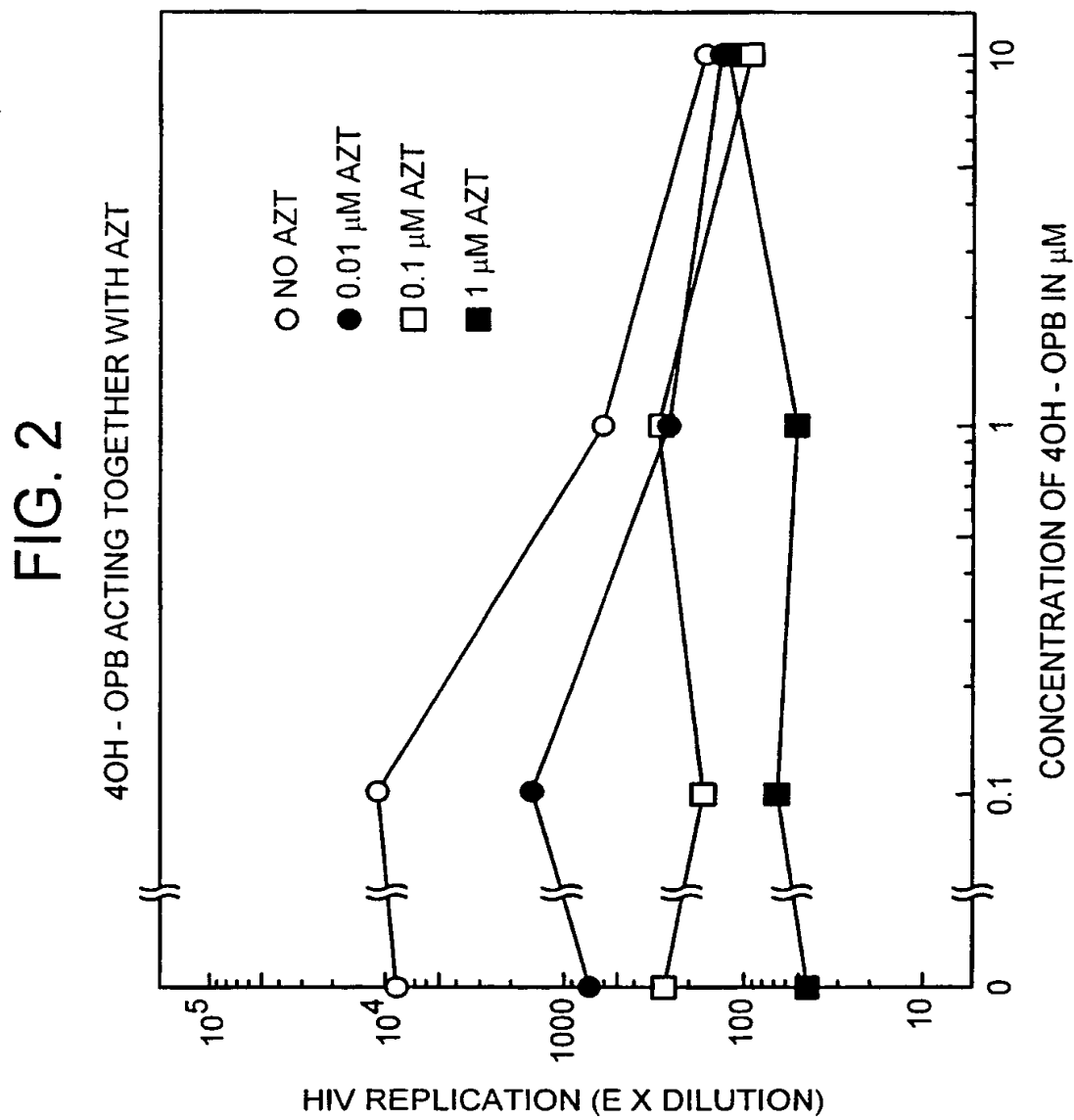
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25. A method of claim 24 wherein said disease is selected from Addison's disease, Behçet's syndrome, diabetes mellitus, haemolytic anaemia, lupus erythematosus, multiple sclerosis, myasthenia gravis, pernicious anaemia, polyglandular deficiency, polymyositis, dermatomyositis, testicular failure, thrombocytopenic purpura, Crohns disease, ulcerative colitis and rheumatoid arthritis.

26. A method of claim 24 wherein said tissue rejection is tissue rejection following transplant.

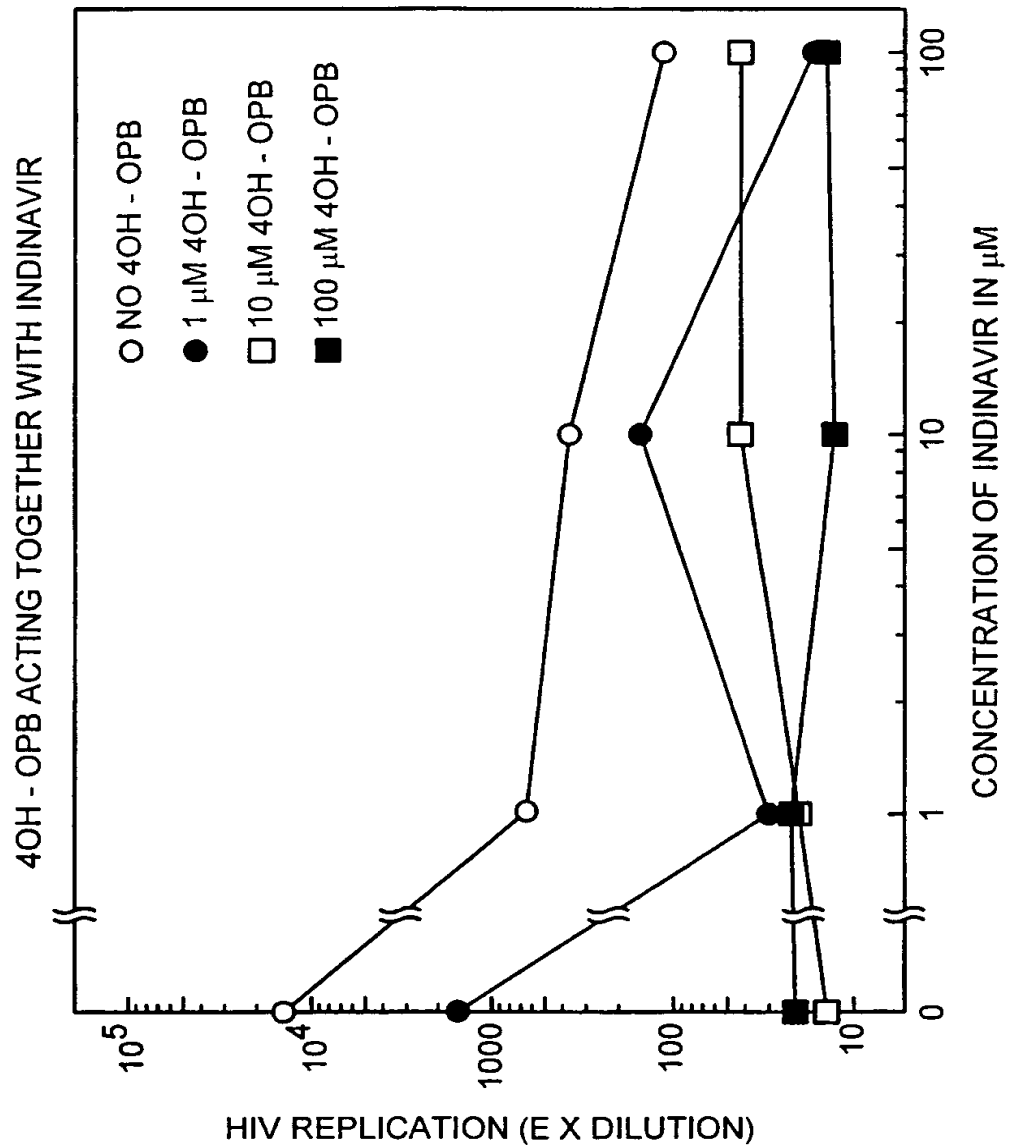


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FIG. 3



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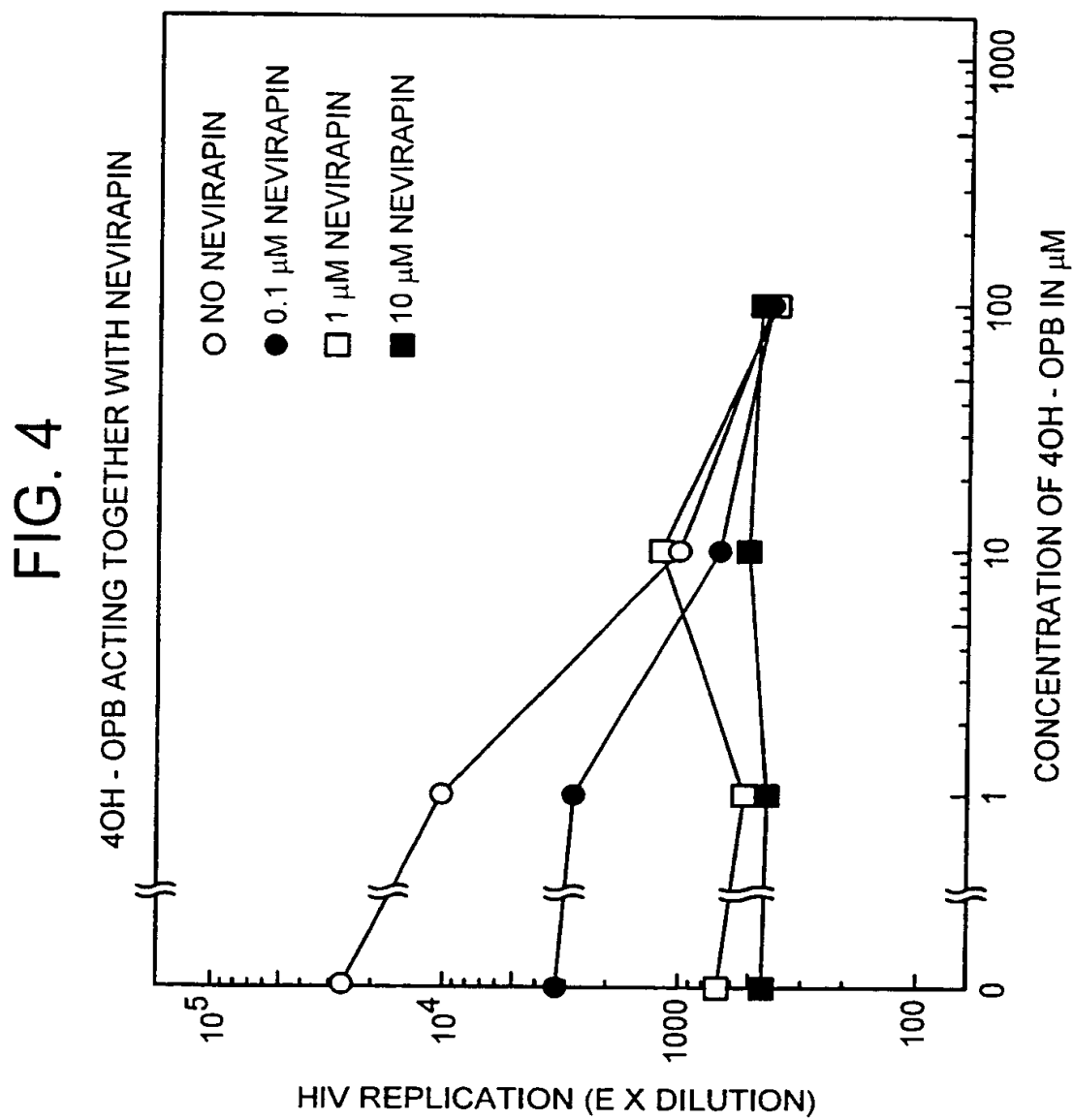
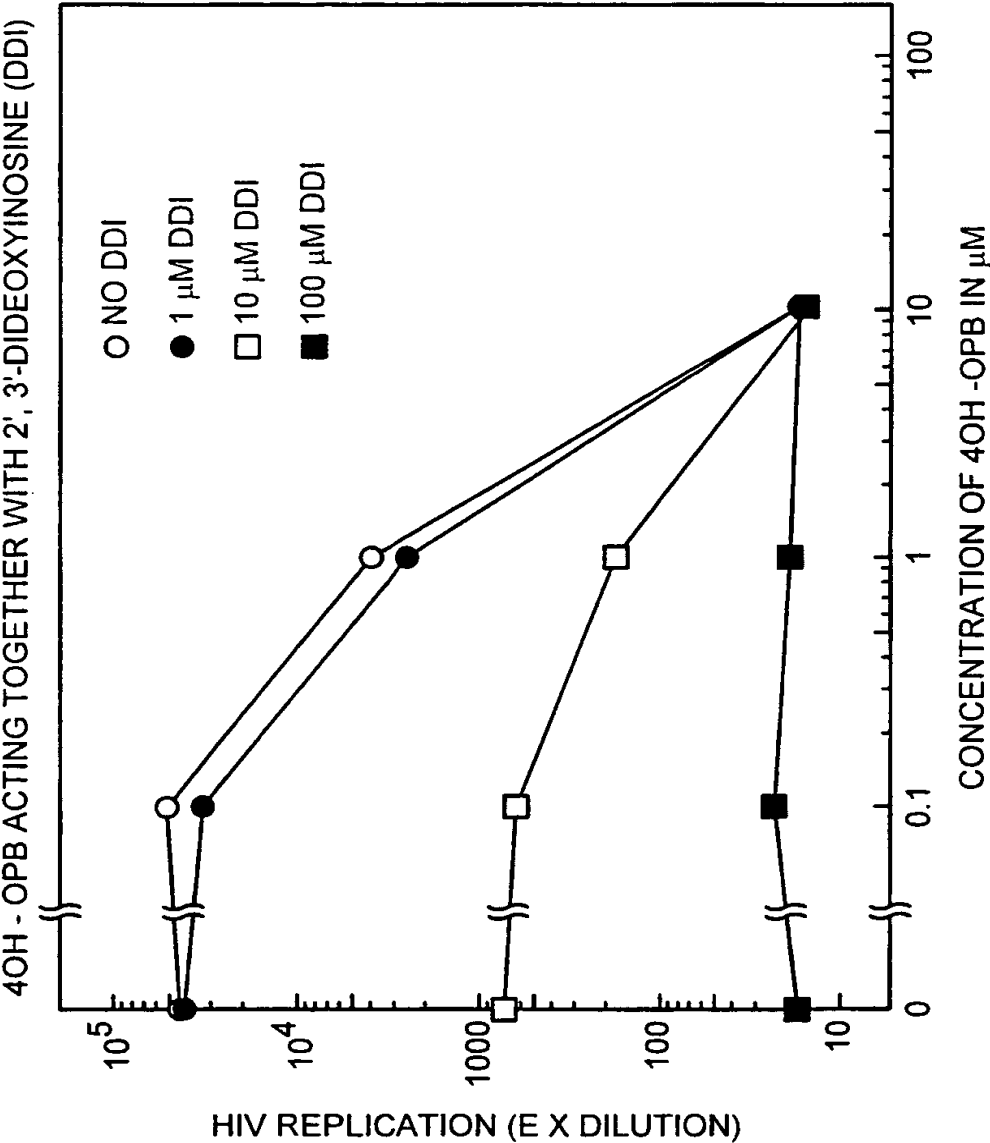


FIG. 5



# INTERNATIONAL SEARCH REPORT

Internat'l Application No  
PCT/GB 00/02513

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D231/32 C07D231/30 A61K31/4152 A61P31/08 A61P37/06

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	M. F. HUGHES ET AL.: MOLECULAR PHARMACOLOGY, vol. 34, no. 2, 1988, pages 186-93, XP000925977 page 186, summary; page 191, scheme 1; page 191-192	1,2,13, 14,16, 17,19, 21,22
X	--- P. S. PORTOGHESE ET AL.: BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 63, no. 3, 1975, pages 748-55, XP000925976 page 748 page 751 -page 752 page 754, figure 2 ---	13,14, 17,20,22
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Hass, C

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